Stereoselective Metal-Catalyzed Transformations for Carbon-Boron Bond Formation and Carbon-Nitrogen Bond Cleavage.

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Doctoral Thesis

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A Bea y a mis padres. Por todo.

This Doctoral Thesis has been developed in the Organic Chemistry Department at Universidad Autónoma de Madrid, under the supervision of Dr. Mariola Tortosa Manzanares and Dr. Alejandro Parra Sanchez.

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LIST OF ABBREVIATIONS

9-BBN	9-Borabicyclo[3.3.1]nonane
Ac	Acetate
acac	Acetylacetone
Ad	Adamantyl
Alk	Alkyl
aq	aquous
Ar	Aryl
BenzP*	(*R*,*R*)-(+)-1,2-Bis(t-butylmethylphosphino)benzene
Bn	Benzyl
Boc	*tert*-Butoxycarbonyl
B_2pin_2	Bis(pinacolato)diboron
Bphen	Bathophenanthroline
bpy	2,2′-Bipyridine
br	Broad
Bu	Butyl
CataCXiumABn	Benzyldi-1-adamantylphosphine
cod	Cyclooctadiene
Cp	Cyclopentadienyl
CSA	Camphorsulfonic acid

Cu-AAA	Copper-catalyzed asymmetric allylic alkylation
Cy	Cyclohexyl
d	doublet
DABCO	1,4-diazabicyclo[2.2.2]octane
dba	Dibenzylideneacetone
DCE	1,2-Dichloroethane
DCM	Dichloromethane
DFT	Density Functional Theory
DIBAL-H	Diisobutylaluminium hydride
DIEA	N,N-Diisopropylethylamine
DIPA	Diisopropylamine
dippf	1,1'-Bis(di-*i*-propylphosphino)ferrocene
DMA	Dimethylacetamide
DMAP	4-(Dimethylamino)pyridine
DME	Dimethoxyethane
DMF	Dimethylformamide
DMP	Dess–Martin periodinane
DMSO	Dimethyl sulfoxide
DPEPhos	Bis[(2-diphenylphosphino)phenyl] ether
dppbenzene	1,2-Bis(diphenylphosphino)benzene

dppe	1,2-Bis(diphenylphosphino)ethane
dppp	1,3-Bis(diphenylphosphino)propane
d.r.	Diastereomeric ratio
dtbbpy	4,4′-Di-tert-butyl-2,2′-dipyridyl
E	Electrophile
EDG	Electron-donating group
ee	Enantiomeric excess
EI	Electronic Impact
e.r.	Enantiomeric ratio
es	Stereospecificity
ESI	Electrospray
Et	Etyl
EWD	Electron-withdrawing group
FAB	Fast atom bombardment
FG	Functional Group
GC	Gas chromatography
HBpin	Pinacolborane
Het	Heteroaryl
Hex	Hexyl
HPLC	High-pressure liquid chromatography
HRMS	High Resolution Mass Spectrometry

ICy	*N,N′* -Bis(cyclohexylimidazol)-2-ylidene
IMes	N,N′-Bis(2,4,6-trimethylphenyl) imidazol) -2-ylidene
Ipc	Isopinocampheyl
IPr	1,3-Bis(2,6-diisopropylphenyl)imidazol-2-ylidene
L	Ligand
L*	Chiral Ligand
LDA	Lithium diisopropylamide
liq	Liquid
m	Multiplet
mCPBA	*meta*-Chloroperoxybenzoic acid
Me	Metyl
MeCN	Acetonitrile
mp	Melting point
MS	Molecular sieves
Ms	Mesyl
MOM	Methoxymethyl
MW	Microwave
NaBArF	Sodium tetrakis[3,5-bis(trifluoromethyl) phenyl] borate
NHC	*N*-Heterocyclic Carbene

NMP	N-Methyl-2-pyrrolidone
NMR	Nuclear Magnetic Resonance
NOE	Nuclear Overhauser effect
n-Pr	Propyl
Nu	Nucleophile
PCC	Pyridinium chlorochromate
Ph	Phenyl
PhthN	Phthalimide
pin	Pinacol
PMB	p-Methoxybenzyl
PMP	*p*-methoxyphenyl
PMP	Pentamethylpiperidine
ppy	2-phenylpyridine
Py	Pyridine
q	Quartet
QuinoxP*	(*R*,*R*)-(–)-2,3-Bis(tert-butylmethylphosphino)
quint	Quintuplet
(*R*)-BINAP	(*R*)-(+)-(1,1′-Binaphthalene-2,2′-diyl)bis(diphenylphosphine)
(*R*)-Difluorphos	*R*-(+)-5,5'-Bis(diphenylphosphino)-2,2,2',2'-tetrafluoro-4,4'-bi-1,3-benzodioxole

(*R*)-DM-Segphos	(*R*)-(+)-5,5′−Bis[di(3,5-xylyl)phosphino]-4,4′-bi-1,3-benzodioxole
(*R*)-DTBM-Segphos	(*R*)-(−)-5,5′-Bis[di(3,5-di-tert-butyl-4-methoxyphenyl)phosphino]-4,4′-bi-1,3-benzodioxole
rt	Room temperature
r.r.	Regioselective ratio
(*R*,*R*)-Me-DuPhos	(–)-1,2-Bis[(2R,5R)-2,5-dimethylphospholano]benzene
(*R*,*R*)-Taniaphos	(R_P)-1-Dicyclohexylphosphino-2-[(*R*)-α-(dimethylamino)-2-(dicyclohexylphosphino)benzyl]ferrocene
(R)-Tol-BINAP	(*R*)-(+)-2,2′-Bis(di-p-tolylphosphino)-1,1′-binaphthyl
s	Singlet
SET	Single electron transfer
sept	septuplet
sex	sextet
SFC	Supercritical Fluid Chromatography
SPhos	2-Dicyclohexylphosphino-2′,6′-dimethoxybiphenyl
SPS	Solvent Purification System
(*S*,*S*)-BDPP	(2*S*,4*S*)-2,4-Bis(diphenylphosphino) pentane

t	triplet
t-amyl	2-methylbutyl
TBAF	Tetra-*n*-butylammonium fluoride
TBS	*tert*-Butyldimethylsilyl
t-Bu	*tert*-Butyl
TC	thiophene-2-carboxylate
Tf	Triflate
THF	Tetrahydrofurane
TLC	Thin layer chromatography
TMEDA	*N*,*N*,*N*',*N*'-Tetramethylethylendiamine
TMS	Trimethylsilyl
Tol	Tolyl
Ts	Tosyl
ttbtpy	4,4',4''-tri-*tert*-butyl terpyridine
Xantphos	4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene

SUMMARY

In the first chapter we have developed an enantioselective copper-catalyzed desymmetrization of meso-cyclobutenes for the synthesis of enantiomerically enriched cyclobutylboronates. This was the first catalytic enantioselective synthesis of this family of compounds. Through this methodology we have prepared a broad scope of cyclobutanes with high levels of diastereo- and enantioselectivity with up to four stereogenic centers.We have also developed some strategies to synthetize useful synthetic intermediates from the cyclobutylboronates.

In the second chapter of this Doctoral Thesis we have developed a stereospecific copper-catalyzed substitution reaction of propargylic ammonium salts with aryl Grignard reagents. The reaction was completely α-regioselective and stereospecific. Also, the functional group tolerance of the reaction is excepcional. In addition, no added ligand was needed, and we simply used an inexpensive copper salt. In the second part of this chapter, we developed a strategy for the synthesis of enantiomerically enriched allenes using alkyl Grignard reagents instead of aryl Grignard reagents. With this strategy we bypassed the problem of the allene racemization when alkyl magnesium halides are used.

In the last chapter of this thesis, we have developed a new methodology for the allyl-allyl cross-coupling reaction between allylic carbonates or ammonium salts and allyl boronates. The reaction was completely regioselective and stereospecific and we have observed complete inversion in the configuration of the chiral center. We have also developed strategies for the selective functionalization of the different double bonds

RESUMEN

En el segundo capítulo, se ha desarrollado el primer método enantioselectivo catalizado por cobre para la desimetrización de ciclobutenos, logrando la síntesis de ciclobutilboronatos quirales. Esta metodología fue la primera catalítica enantioselectiva de esta clase de compuestos. Los ciclobutilboronatos obtenidos presentaron altos niveles de diastereo- y enantioselectividad con hasta 4 centros estereogénicos en la molécula. También desarrollamos métodos para sintetizar valiosos intermedios sintéticos a partir de los productos obtenidos.

En el tercer capítulo de la presente Tesis Doctoral hemos desarrollado una metodología para la sustitución nucleófila estereoespecífica con reactivos de Grignard arílicos de sales de amonio propargílicas catalizada por cobre. La reacción fue completamente regioselectiva y enantioespecífica. Además, la reacción presento una alta compatibilidad con diversos grupos funcionales sin la necesidad de añadir un ligando. En la segunda parte de este capítulo, utilizamos esta estrategia para la síntesis de alenos enantioméricamente enriquecidos usando reactivos de Grignard alquílicos en lugar de arílicos. Mediante esta estrategia conseguimos evitar la racemización que presentan este tipo de reacciones.

En el último capítulo de esta Tesis Doctoral, hemos desarrollado una nueva metodología para el acoplamiento alilo-alilo entre carbonatos o sales de amonio alílicas y boronatos alílicos. La reacción fue completamente regioselectiva y enantioespecífica y observamos una inversión completa del centro quiral. También, hemos desarrollado estrategias para la funcionalización selectiva de los diferentes dobles enlaces que se forman en la reacción.

Chapter 1

INTRODUCTION

1. INTRODUCTION

Chirality is defined as "The geometric property of a rigid object (or spatial arrangement of points or atoms) of being non-superposable on its mirror image; such an object has no symmetry elements of the second kind (a mirror plane, $\sigma = S_1$, a centre of inversion, $i = S_2$, a rotation-reflection axis, S_{2n}). If the object is superposable on its mirror image the object is described as being achiral".[1] A French chemist and biologist known as Louis Pasteur discover chiral chemistry when he separated by hand the two enantiomers of sodium ammonium tartrate in 1848.[2] An easy example of a chiral molecule could be the aminoacid alanine (**Figure *1-1***). These molecules are enantiomers and they have identical chemical and physical properties. However, if they are in a chiral environment there could be important differences in their properties.

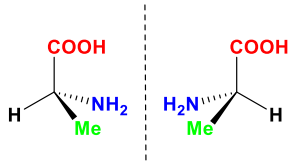


Figure 1-1: Mirror images of aminoacid alanine.

Life depends on chiral recognition, because the interaction between living systems and enantiomers are usually different. Metabolic processes and biological responses occur because enzymes or other natural binding places

[1] McNaught, A.D.; Wilkinson, A. *IUPAC, Compendium of Chemical Terminology*, 2nd ed. Blackwell Scientific Publication, Oxford, 1997.

[2] Challener CA. *Overview of chirality. In: Chiral drugs.* 1st ed. Ashgate Publisher. Aldershot, 2001; pp. 3-14.

only recognize a specific molecular geometry. This differences in the properties of two enantiomers in a chiral environment are the reason why asymmetric synthesis has become a main field inside organic chemistry during the last decades. Around 60% of the commercial drugs have at least one stereogenic center in their structure and sometimes the configuration of this center has a critical effect in the pharmaceutical properties of the drug. Pharmaceutical control agencies compel pharmaceuticals companies to synthetize all the possible stereoisomers of a drug to test for possible side effect and to determine which isomer is the biologically active.[3] The case of Thalidomide is well-known because it caused ten thousand infants to born with limbs malformations between 1957 and 1963. Only half of them survived. The problem was that thalidomide was sold as a racemate, and one of the enantiomers did treat nauseas and morning sickness in pregnant women but the other one is a teratogenic agent and cause phocomelia in the babies. Dextropropoxyphene is a well-known analgesic, but his enantiomer is an anticough drug.[4]

However, stereoisomers are not only important in the pharmaceutical field. (*S*)-carvone smells like caraway, but its enantiomer smells like spearmint, so this fact is really important for perfumes manufactures (**Figure *1*-*2***).[3]

[3] Nguyen, L.A.; He, H.; Pham-Huy, C. *Int. J. Biomed. Science* **2006**, 85-100.
[4] Drayer, D.E. *Clin. Pharmacol. Ther.* **1986**, *40*, 125.

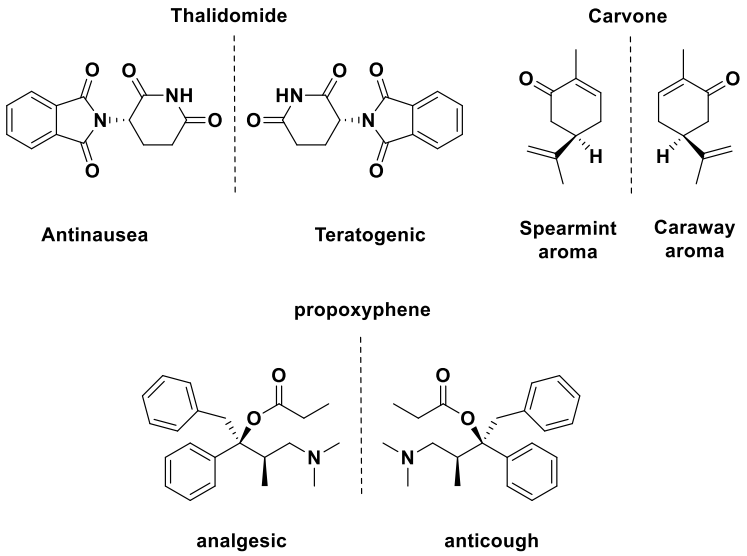
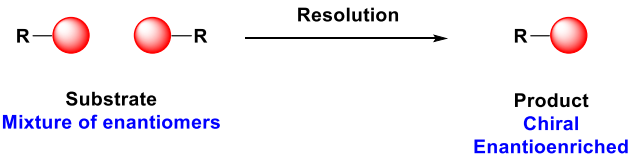


Figure 1-2: Different properties of enantiomers.

There are two main methodologies to obtain enantiopure compounds. Traditionally, enantiomerically enriched compounds were obtained through the separation of both enantiomers from the corresponding racemate. This was achieved either by crystallization or kinetic resolution (**Scheme *1-1*¡Error! No se encuentra el origen de la referencia.**).



Scheme 1-1: Resolution of a racemate to obtain an enantiomerically enriched compound.

More recently, the advances in chiral chromatography allows for the separation of enantiomers by different techniques, as high-pressure liquid chromatography (HPLC) or gas chromatography (GC).[5] However, the separation of the racemate, implies that at least 50% of the compound is lost. Because of this fact, asymmetric synthesis has arisen in the last decades as the preferred methodology to obtain enantiomerically enriched compounds.

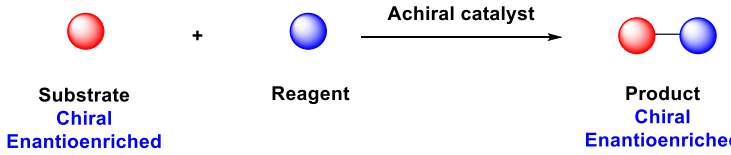
Asymmetric synthesis is a method for preparation of chemical compounds which aims to bias the synthesis in favor of producing one stereoisomer over another stereoisomer. Diastereomeric transition states must occur during the formation of the product in order to produce a different rate of reaction for the different stereoisomers. To form this diastereomeric transition states, a non-racemic chiral compound must be involved in the reaction. This compound could be a reagent or a chiral catalyst. We can divide asymmetric catalytic synthesis on various groups:

- The substrate is a non-racemic chiral compound. The formation of the new formed stereogenic center goes through a diastereomeric transition state where the different rates of reaction determine which isomer is formed preferentially (**Scheme *1-2***). In this section are included stereospecific reactions and asymmetric induction. By definition, stereospecificity is the property of a reaction mechanism that leads to different stereoisomeric reaction products from different stereoisomeric reactants, or which operates on only one (or a subset) of the stereoisomers.[6] On the other hand, asymmetric induction describes the preferential formation in a chemical reaction of one enantiomer or diastereoisomer over the other as a result of the influence of a chiral

[5] Donald, T.H.; Bingyun, L. *Chiral Drug Separation*. In *Encyclopedia of Chemical Processing*. Lee, S. Taylor & Francis, New York, 2007.

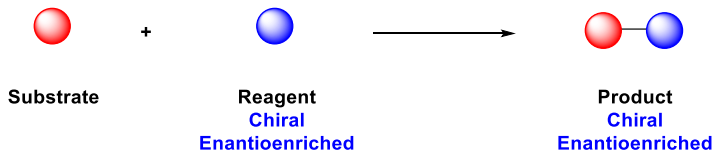
[6] Eliel, E., "*Stereochemistry of Carbon Compound*", McGraw-Hill, 1962 pp 434-436.

feature present in the substrate, reagent, catalyst or environment. Usually, the removal of the asymmetric inductor is needed after the reaction. The main problem of this family of reaction is that an stochiometric non-racemic chiral reagent is needed in the reaction.



Scheme 1-2: Asymmetric reaction using a non-racemic substrate.

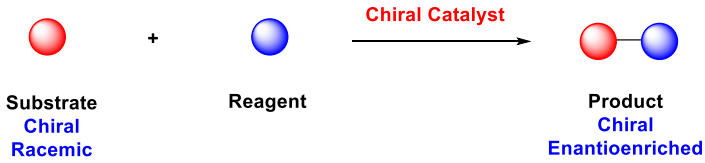
- The reagent is a non-racemic chiral compound. In this case is the reagent the one that carries the stereogenic center. This causes that diastereomeric transition states are formed and the isomers are formed at different rates (**Scheme *1-3***). This is a very similar case than the former one, and any explanation and definition described above, applies to this case



Scheme 1-3: Asymmetric reaction using a non-racemic reagent.

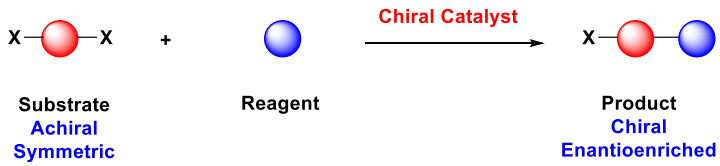
- Enantioselective catalyzed reactions, which we define as reactions in which there is selective formation of one enantiomer over the other as defined by a nonracemic chiral catalyst from achiral or racemic

substrates. Since the catalyst is not consumed in this process it may be used in a substoichiometric quantity potentially improving efficiency and avoiding waste. The catalyst could be metal-based catalyst or an organocatalyst. The importance of asymmetric catalysis could be hihjlighted for the 2011 Nobel Prize to Professors William R. Knowles and Ryoji Noyori "for their work on chirally catalyzed hydrogenation reactions" and K. Barry Sharpless "for their work on chirally catalyzed oxidation reactions" (**Scheme *1-4***).



Scheme 1-4: Enantioselective catalyzed reactions.

- Enantioselective catalyzed desymmetrization, which we defined as reaction where a prochiral starting material (meso-compound) is desymmetrized. The new bond formation is used to break the symmetry through a process controlled by the chiral catalyst (**Scheme *1-5***). I will detail this in the next section.



Scheme 1-5: Catalized desymmetrization reactions.

A comprehensive review of the literature regarding asymmetric synthesis exceeds the scope of the introduction of this chapter. Therefore, only a brief section about metal catalyzed desymmetrization reactions will be explained.

1.1. Metal-Catalyzed Desymmetrization Reactions.

The first project of the present doctoral Thesis is the copper-catalyzed desymmetrization of *meso*-cyclobutenes. A *meso* molecule is defined as "an achiral member(s) of a set of diastereomers which also includes one or more chiral members".[7] Unlike prochiral compounds, they contain pairs of chiral elements, but remain achiral due to the existence of a symmetry element (**Figure *1-3***).

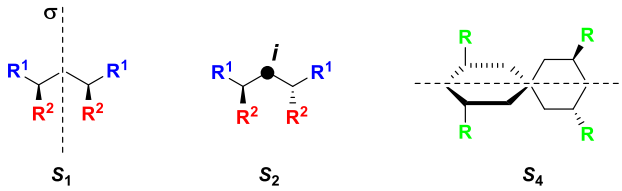


Figure 1-3: Symmetry elements in *meso*-compounds.

In a synthetic sequence, chiral compounds usually constitute the most expensive reagents. Therefore, the use of stochiometric amounts of enantiomerically enriched substrates or reagents is unfavored. Enantioselective catalysis solves this problem using only small amounts of the chiral component in the reaction. The use of meso-compounds in enantioselective catalytic desymmetrization reactions allows for the preparation of molecules with several stereogenic centers in only one step of synthesis.

[7] Moss, G. P. *Pure Appl. Chem.* **1996**, *68*, 2193-2222.

The desymmetrization step could be achieved by the use of enzymes[8] or organocatalysis[9] but in the following pages we will explain some illustrative examples of metal-catalyzed desymmetrizations.[10]

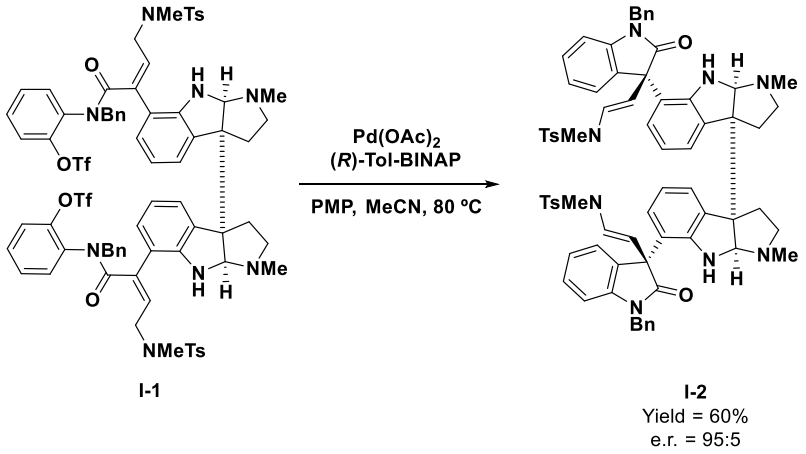
In 2002, Overman and coworkers reported a concise synthesis of quadrigemine C.[11] As key step of the synthesis they proposed a desymmetrization of a complex *meso* intermediate **II-1**. The strategy consisted in a double intramolecular heck reaction catalyzed by a palladium chiral complex (**Scheme *1*-*6***).

[8] For a review see: Garcia-Urdiales, E.; Alfonso, I.; Gotor, V. *Chem. Rev.* **2011**, *111*, PR110-PR180. For illustrative examples in total synthesis see: a) Baran, P. S.; Li, K.; O'Malley, D.P.; Mitsos, C. *Angew. Chem. Int. Ed.* **2006**, *45*, 249-252. b) Göksel, H.; Stark, C.B.W. *Org. Lett.* **2006**, *8*, 3433-3436. c) Candy, M.; Audran, G.; Bienaymé, H.; Bressy, C.; Pons, J.M. *J. Org. Chem*. **2010**, *75*, 1354-1359.

[9] For a review see: Borissov, A.; Davies, T.Q.; Ellis, S.R.; Fleming, T.A.; Richardson, M.S.W.; Dixon, D.J. *Chem. Soc. Rev.* **2016**, *45*, 5474-5540. For illustrative examples in total synthesis see: a) Chandler, C. L.; List, B. *J. Am. Chem. Soc.* **2008**, *130*, 6737-6739. b) Merad, J.; Borkar, P.; Bouyon-Yenda, T.; Roux, C.; Pons, J.M.; Parrain, J.L.; Chuzel, O.; Bressy, C. *Org. Lett.* **2015**, *17*, 2118-2121.

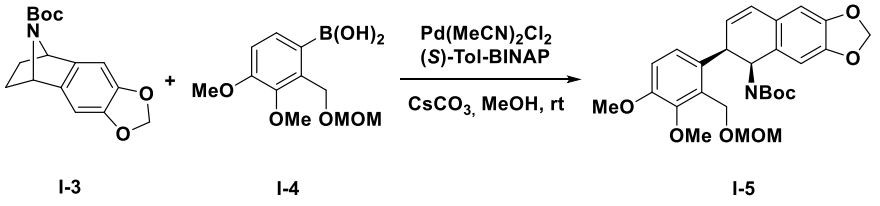
[10] For a review see: a) Ward, R.S. *Chem. Soc. Rev.* **1990**, *19*, 1-19. b) Poss, C.S.; Schreiber, S.T. *Acc. Chem. Res.* **1994**, *27*, 9-17. c) Zeng, X.P.; Cao, Z.Y.; Wang, Y.H.; Zhou, F.; Zhou, J. *Chem. Rev.* **2016**, *116*, 7330-7396. d) Merad, J.; Candy, M.; Pons, J.M.; Bressy, C. *Synthesis* **2017**, *49*, 1938-1954.

[11] Lebsack, A.D.; Link, J.T.; Overman, L.E.; Stearns, B.A. *J. Am. Chem. Soc.* **2002**, *124*, 9008-9009.



Scheme 1-6: Desymmetrization step in the total synthesis of Quadrigemine C.

In 2007, Lautens and coworkers reported the very first enantioselective synthesis of (+)-homochelidone.[12] The key step of the synthesis was the enantioselective ring opening of the meso compound **I-3** by cross-coupling with boronic acid **I-4** using a chiral palladium complex (**Scheme *1-7***).



Scheme 1-7: Palladium catalyzed desymmetrization in the synthesis of (+)-homochelidone.

[12] McManus, H.; Fleming, M.J.; Lautens, M. *Angew. Chem. Int. Ed.* **2007**, *46*, 433-436.

Chapter 2

SYNTHESIS OF CYCLOBUTYLBORONATES

2. SYNTHESIS OF CYCLOBUTYLBORONATES.

2.1. Background.

2.1.1. General Overview of Organoboron Compounds.

Located in the fifth position of the periodic table, boron has a ground state electron configuration of $1s^2 2s^2 2p^1$ and therefore three valence electrons. Commonly, boron forms trivalent neutral compounds with and empty *p*-orbital. This kind of compounds are electron deficient, and as boron is sp^2 hybridized, are isoelectronic with carbocations (**Figure *2-1***).[1]

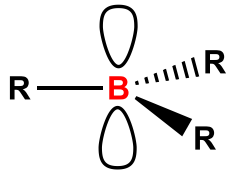


Figure 2-1: General structure of organoboron compounds.

Organoboron compounds present a C-B bond in their structure. They must be synthetized in the laboratory, because C-B bonds do not exist in nature. It was mid XIX century when Frankland and Duppa,[2] synthetized and isolated the first boronic acids, although organoboron compounds were not used until much later.

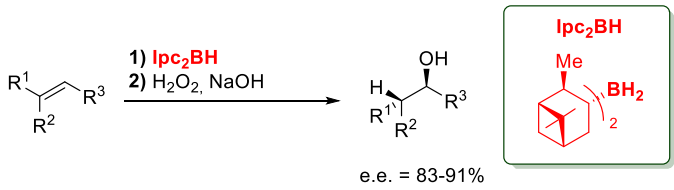
[1] Ingleson, M. J. Fundamental and Applied Properties of Borocations. En *Synthesis and Application of Organoboron Compounds*; Fernández, E., Whiting, A. Ed.; Springer International Publishing: Switzerland, 2015; pp 39-71.

[2] a) Frankland, E.; Duppa, B. F. *Justus Liebigs Ann. Chem.* **1860**, *115*, 319-322; b) Frankland, E.; Duppa, B. F. *Proc. R. Soc. Lond.* **1860**, *10*, 568-570; c) Frankland, E.; Duppa, B. F. *J. Chem. Soc*. **1862**, *15*, 363-381.

In the early XX century, Alfred Stock developed a series of vacuum techniques to prepare the very first boron hydrides, starting off the field of borane chemistry. They synthetize B_2H_6, B_4H_{10}, B_5H_9 and B_6H_{10}, which proved to be volatile and explosive.[3] In 1972, fascinated by the nature of these compounds, Lipscomb studied by X-ray diffraction the structure of boranes, developing a new theory of chemical bonding, essential to understand the nature of boranes. His work was recognized with the Nobel Prize in 1976.[4]

But it was the organic chemistry community the one that developed the first useful applications of organoboron compounds and also, take the challenge of developing boron chemistry. In 1956, Professor Herbert C. Brown published the very first hydroboration of alkenes.[5] After the discovery of the so called "Brown Hydroboration", a large number of reactions using organoboron compounds have been reported. In 1961, Brown also established one of the bases of asymmetric synthesis succeeding in the hydroboration of different olefins with diisopinocampheylborane. At that time, the stereoselectivities obtained in this reaction were only paired with some enzymatic processes (***Scheme 2-1***).[6]

[3] Stock, A.; Massenez, C. *Eur. J. Inorg. Chem.* **1912**, *45*, 3539-3568.
[4] Lipscomb, W. N. *Pure. Appl. Chem.* **1972**, *29*, 493-511.
[5] a) Brown, H. C.; Subba Rao, B. C. *J. Am. Chem. Soc.* **1956**, *78*, 5694-5695. (b) Wang, Z. Brown Hydroboration. In *Comprehensive Organic Name Reactions and Reagents*; John Wiley & Sons: Hoboken, 2009; pp 536-543.
[6] Brown, H. C.; Zweifel, G. *J. Am. Chem. Soc.* **1961**, *83*, 486-487.



Scheme 2-1: First asymmetric hydroboration of alkenes.

Professor Brown's career was devoted to boron chemistry. He developed a large number of methodologies for the synthesis of C-B bonds, a highly versatile bond, which can be converted into C-O, C-N, C-C or C-X bond afterwards.[7] Herbert C. Brown was awarded with the Nobel Prize in Chemistry in 1979 for his contributions to this field.

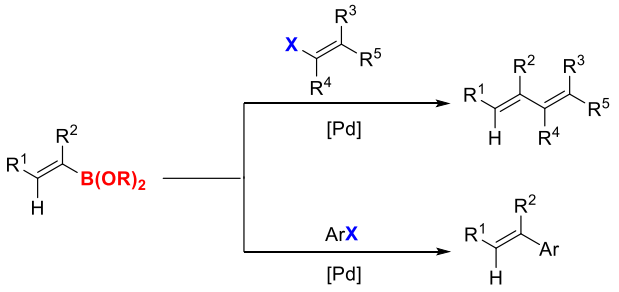
In the 70's, with the development of palladium catalyzed cross-coupling reaction, several groups were trying to take advantage of the facile synthesis of alkenyl boranes from alkynes, to use them in cross-coupling reactions. But it was not until 1979, when Professor Akira Suzuki realized that organic groups in organoboranes have weak carbanion character. Because of this character, transmetalation between organoboranes and palladium complexes does not occur efficiently. He notice that, if organoborates, obtained from organoboranes and a base, were used instead, transmetalation took place smoothly.[8] Afterwards, they realize that boronic acids and esters presented several advantages over boranes (**Scheme *2-2***). They are more stable and easier to handle, less polar and less reactive.[9] In

[7] Brown, H. C. *Organic Syntheses via Boranes*; Wiley: New York, 1975.

[8] a) Miyaura, N.; Yamada, K.; Suzuki, A. *Tetrahedron Lett.* **1979**, *36*, 3437-3440. b) Miyaura, N.; Suzuki, A. *J. Chem. Soc., Chem. Commun.* **1979**, 866-867

[9] a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457-2483. b) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147-168. c) Martin, R.; Buchwald, S. L. *Acc. Chem. Res.* **2008**, *41*, 1461-1473. d) Sun, H. Y.; Hall, D. G. At the Forefront of the Suzuki-Miyaura Reaction: Advances in Stereoselective Cross-Couplings. In *Synthesis and Application of Organoboron Compounds;* Fernández, E., Whiting, A. Ed.; Springer International Publishing:

2010, Professors Richard Heck, EiiChi Negishi and Akira Suzuki were awarded with the Nobel Prize of Chemistry for their contribution to cross-coupling reactions.



Scheme 2-2: Suzuki cross-coupling reaction.

In the last two decades, the increasing number of publications about boron chemistry, may indicate a reborn of this chemistry. Boron have found many interesting applications beyond the organic synthesis field. It plays a new role in drug discovery with the approval of anticancer agent Velcade ® and fungicide Kerydin® (***Figure 2-2***), the first drugs in the market with a boron atom in their structure. Also, boron chemistry is presented in polymers,[10] nanotubes[11] and neutron capture therapy (^{10}B). This renaissance of boron chemistry demonstrates that Professor Brown's words are not old

Switzerland, 2015; pp 221-242. e) Hussain, I.; Capricho, J.; Yawer, M. A. *Adv. Synth. Catal.* **2016**, *358*, 3320-3349. f) Das, P.; Linert, W. *Coord. Chem. Rev.* **2016**, *311*, 1-23. g) Almond-Thynne, J.; Blakemore, D. C.; Prydeb, D. C.; Spivey, A. C. *Chem. Sci.* **2017**, *8*, 40-62. h) Sydnes, M. O. *Catalysts* **2017**, *7*, 35-48. i) Hooshmand, S. E.; Heidari, B.; Sedghi, R.; Varma, R. S. *Green Chem*. **2019**, *21*, 381-405.

[10] a) Matsumi, N.; Naka, K.; Chujo Y. *J. Am. Chem. Soc.* **1998**, *120*, 5112-5113. b) Matsumi, N.; Naka, K.; Chujo Y. *J. Am. Chem. Soc.* **1998**, *120*, 10776-10777. c) Entwistle, C. D.; Marder, T. B. *Angew. Chem. Int. Ed.* **2002**, *41*, 2927-2931. d) Brooks, W. L. A.; Sumerlin, B. S. *Chem. Rev.* **2016**, *116*, 1375-1397.

[11] a) Barth, R. F.; Soloway, A. H.; Brugger, R. M. *Cancer Invest.* **1996**, *14*, 534-550. b) Yura, Y.; Fujita, Y. *Oral Science International* **2013**, *10*, 9-14.

fashioned: "*a new continent has been discovered – it requires settlers to develop its riches to contribute to mankind*."

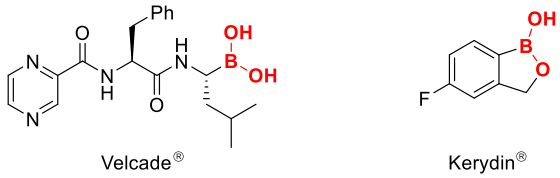


Figure 2-2: Boron-containing drugs in the market.

2.1.2. Boronic Acids and Derivatives.

Trivalent boron-containing molecules that possess one carbon-based substituent and two hydroxyl groups are known as boronic acids and they are important intermediates in organic synthesis.[12] If instead of two hydroxyl groups they have two alkoxides, they are known as boronic esters or boronates. The later are generally easier to handle and less polar than boronic esters, but they are less reactive. A wide selection of boronic esters can be found in organic synthesis. In fact, some of them, bearing a chiral alkoxide, can be used as inductors in stereoselective transformations.[13] Among the most widely used boronic esters are ethylenglycol (Beg), pinacol (Bpin), neopentylglycol (Bnep), hexyleneglycol (Bheg), pinanediol (Bpnd) and cathecol (Bcat) derivatives. Usually, stability of this species increases in hindered cyclic boronates as Bpin. A special case is Bcat, which is very sensible and prone to hydrolysis. The reason behind this behavior is the conjugation between the oxygen atom and the benzene ring.

[12] a) Meng, F.; McGrath, K. P.; Hoveyda, A. H. *Nature* **2014**, *513*, 367-374. b) Antonio, J. P. M.; Russo, R.; Carvalho, C. P.; Cal, P. M. S. D.; Gois, P. M. P. *Chem. Soc. Rev.* **2019**, *48*, 3513-3536.

[13] a) Ramachandran, P. V.; Brown, H. C. Recent Advances in Borane Chemistry. In *Organoboranes for Syntheses*, ACS Symposium Series 783; American Chemical Society: Washington, DC, 2001; pp 1-15. b) Matteson, D. S. *Tetrahedron* **1998**, *54*, 10555-10607.

That confers the boron atom a higher Lewis acidity. Beyond these, recently diethanolamine (BDEA) and *N*-methyliminodiacetic acid (BMIDA) have been employed as alternative protecting groups. Moreover, 1,8-diaminonaphthalene (Bdan) has also been used, providing a less Lewis acidic boron atom (**Figure *2-3***).[14]

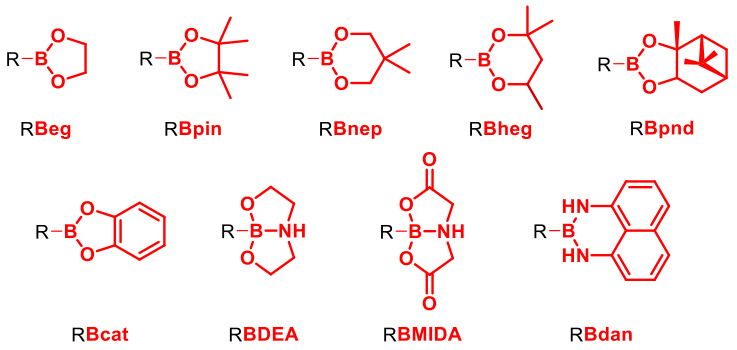


Figure 2-3: Most commonly used boronic esters.

The partial donation of the oxygen electron pairs to the empty p-orbital of the boron atom confers the B-O bond a partial double bond character and thus, making it around 40 Kcal/mol stronger than C-O bond (130 versus 92 Kcal/mol).[15] In boronic esters, with two oxygen atoms attached to the boron center, the vacant orbital of boron only can accept one π dative bond, so the electronic structure can be explained by two resonance forms (**Figure *2-4***).[14]

[14] Hall, D. G. *Boronic Acids: Preparation and Application in Organic Synthesis, Medicine and Materials*, 2nd ed.; Wiley-VCH: Boston, 2011.
[15] Sana, M.; Leroy, G.; Wilante, C. *Organometallics* **1991**, *10*, 264-270.

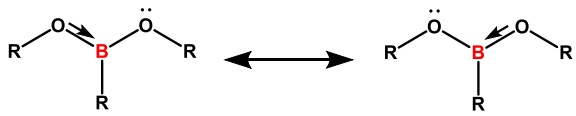


Figure 2-4: Resonance forms of π dative bond intermediates.

Traditional approaches to synthetize boronic esters are based on organometallic reagents such as lithium compounds[16] or Grignard reagents.[17] However, the lack of compatibility of these reagents with several functional groups make this approach impossible in some cases. It was not until 1995 that Professor Miyaura finally solved this problem. He described the palladium catalyzed cross-coupling of bis(pinacolato)diboron with aryl bromides or iodines, obtaining the correspondent aryl boronates (**Scheme *2-3***).[18] The Miyaura borylation possesses a broad scope and the compatibility of functional groups is no longer an issue. The reaction can also be performed with vinyl,[19] aryl,[20] allyl[21] or benzyl[22] halides or triflates.

[16] Brown, H. C.; Cole, T. E. *Organometallics* **1983**, *2*, 1316-1319.

[17] a) Gilman, H.; Vernon, C. *J. Am. Chem. Soc.* **1926**, *48*, 1063-1066; b) Clary, J. W.; Rettenmaier, T. J.; Snelling, R.; Bryks, W.; Banwell, J.; Wipke, W. T.; Singaram, B. *J. Org. Chem.* **2011**, *76*, 9602-9610.

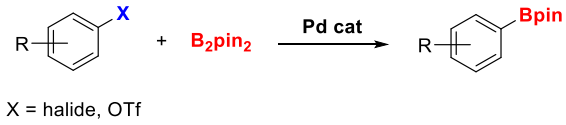
[18] a) Ishiyama, T.; Murata, M.; Miyaura, N. *J. Org. Chem.* **1995**, *60*, 7508-7510. b) Ishiyama, T.; Itoh, Y.; Kitano, T.; Miyaura, N. *Tetrahedron Lett.* **1997**, *38*, 3447-3450. c) Ishiyama, T.; Miyaura, N. *J. Organomet. Chem.* **2000**, *611*, 392-402. d) Ishiyama, T.; Miyaura, N. *Chem. Rec.* **2004**, *3*, 271-280. e) Kürti, L.; Czakó, B. *Miyaura Boration* In *Strategic Applications of Named Reactions in Organic Synthesis.* 1st edition, Elsevier, London, 2005. pp 296-297. f) Miyaura, N. *Bull. Chem. Soc. Jpn.* **2008**, *81*, 1535-1553.

[19] (a) Takahashi, K.; Takagi, J.; Ishiyama, T.; Miyaura, N. *Chem. Lett*. **2000**, 126-127. (b) Takagi, J.; Takahashi, K.; Ishiyama, T.; Miyaura, N. *J. Am. Chem. Soc*. **2002**, *124*, 8001-8006.

[20] (a) Ishiyama, T.; Itoh, Y.; Kitano, Y.; Miyaura, N. *Tetrahedron Lett.* **1997**, *38*, 3447-3450. (b) Fürstner, A.; Seidel, G. *Org. Lett*. **2002**, *4*, 541-543. (c) Billingsley, K. L.; Barder, T. E.; Buchwald, S. L. *Angew. Chem. Int. Ed*. **2007**, *46*, 5359-5363.

[21] Zhang, P.; Roundtree, I. A.; Morken, J. P. *Org. Lett*. **2012**, *14*, 1416-1419.

[22] Ishiyama, T.; Oohashi, Z.; Ahiko, T. -A.; Miyaura, N. *Chem. Lett*. **2002**, 780-781.



Scheme 2-3: Miyaura Borylation.

The metal-catalyzed hydroboration has become another useful strategy to introduce boronic ester groups in unsaturated compounds, as well as the addition of diboron compounds.[23] Platinum is usually the best performing metal in the addition of diboron compounds;[24] however, other metals such palladium,[25] gold,[26] iridium[27] or rhodium[28] have proven themselves equally useful. The reaction is quite general and all alkynes,[29] alkenes,[30] allenes,[31] carbonyls[32] and imines[33] are feasible substrates for the transformation.

[23] a) Beletskaya, I.; Pelter, A. *Tetrahedron* **1997**, *53*, 4957-5026. b) Crudden, C. M.; Edwards, D. *Eur. J. Org. Chem*. **2003**, 4695-4712. c) Chow, W. K.; Yuen, O. Y.; Choy, P. Y.; So, C. M.; Lau, C. P.; Wong, W. T.; Kwong, F. Y. *RSC Adv.* **2013**, *3*, 12518-12539. d) Neeve, E. C.; Geier, S. J.; Mkhalid, I. A. I.; Westcott, S. A.; Marder, T. B. *Chem. Rev*. **2016**, *116*, 9091-9161. e) Hemmings, D.; Fritemeier, R.; Westcott, S. A.; Santos, W. L.; Steel, P. G. *Chem. Soc. Rev*. **2018**, *47*, 7477-7494.

[24] Ishiyama, T.; Matsuda, N.; Murata, M.; Ozawa, F.; Suzuki, A.; Miyaura, N. *Organometallics* **1996**, *15*, 713-720.

[25] Yang, F. -Y.; Cheng, C. -H. *J. Am. Chem. Soc.* **2001**, *123*, 761-762.

[26] Baker, R. T.; Nguyen, P.; Marder, T. B.; Westcott, S. A. *Angew. Chem., Int. Ed.* **1995**, *34*, 1336-1338.

[27] Xu, L.; Zhang, S.; Li, P. *Chem. Soc. Rev*. **2015**, *44*, 8848-8858.

[28] Nguyen, P.; Coapes, R. B.; Woodward, A. D.; Taylor, N. J.; Burke, J. M.; Howard, J. A. K.; Marder, T. B. *J. Organomet. Chem.* **2002**, *652*, 77-85.

[29] Ishiyama, T.; Matsuda, N.; Miyaura, N.; Suzuki, A. *J. Am. Chem. Soc.* **1993**, *115*, 11018-11019.

[30] a) Ishiyama, T.; Yamamoto, M.; Miyaura, N. *Chem. Commun*. **1996**, 2073-2074. b) Ishiyama, T.; Yamamoto, M.; Miyaura, N. *Chem. Commun.* **1997**, 689-690. c) Iverson, C. N.; Smith, M. R. *Organometallics* **1997**, *16*, 2757-2759.

[31] Ishiyama, T.; Kitano, T.; Miyaura, N. *Tetrahedron Lett.* **1998**, *39*, 2357-2360.

[32] Lawson, Y. G.; Lesley, M. J. G.; Norman, N. C.; Rice, C. R.; Marder, T. B. *Chem. Commun.* **1997**, 2051-2052.

[33] Cameron, T. M.; Baker, R. T.; Westcott, S. A. *Chem. Commun*. **1998**, 2395-2396.

C-H borylation catalyzed by transition metals has become recently a convenient strategy to prepare aryl boronates.[34] This methodology is quite elegant, due to the fact than the use of aryl halides or triflates is no longer require and simple arenes can be used instead. Rhodium,[35] palladium[36] or rhenium[37] are metals that perform well in this transformation, but iridium is the most commonly used catalyst in this borylation.[38] Previously inert bonds such C-F[39] bonds or C-OR[40] bonds can also be activated by metal-catalyzed borylations (**Scheme *2-4***).

[34] a) Ishiyama, T.; Miyaura, N. *J. Organomet. Chem.* **2003**, *680*, 3-11. b) Mkhalid, I. A. I.; Barnard, J. H.; Marder, T. B.; Murphy, J. M.; Hartwig, J. F. *Chem. Rev*. **2010**, *110*, 890-931. c) Ros, A.; Fernández, R.; Lassaletta, J. M. *Chem. Soc. Rev.* **2014**, *43*, 3229-3243.

[35] a) Chen, H. Y.; Schlecht, S.; Semple, T. C.; Hartwig, J. F. *Science* **2000**, *287*, 1995-1997. b) Kawamorita, S.; Miyazaki, T.; Ohmiya, H.; Iwai, T.; Sawamura, M. *J. Am. Chem. Soc.* **2011**, *133*, 19310-19313.

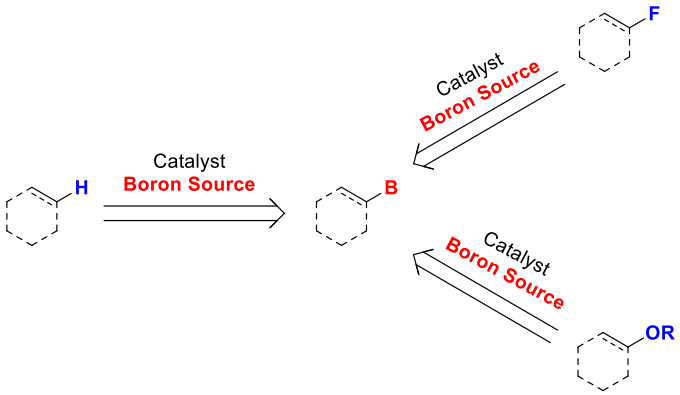
[36] a) Ishiyama, T.; Ishida, K.; Takagi, J.; Miyaura, N. *Chem. Lett.* **2001**, *30*, 1082-1083. b) Dai, H. X.; Yu, J. Q. *J. Am. Chem. Soc.* **2012**, *134*, 134-137. c) Kuninobu, Y.; Iwanaga, T.; Omura, T.; Takai, K. *Angew. Chem. Int. Ed.* **2013**, *52*, 4431-4434.

[37] Chen, H.; Hartwig, J. F. *Angew. Chem. Int. Ed.* **1999**, *38*, 3391-3393.

[38] a) Iverson, C. N.; Smith, M. R., III. *J. Am. Chem. Soc.* **1999**, *121*, 7696-7697. b) Cho, J. Y.; Iverson, C. N.; Smith, M. R. III. *J. Am. Chem. Soc.* **2000**, *122*, 12868-12869. c) Cho, J. -Y.; Tse, M. K.; Holmes, D.; Maleczka, R. E., Jr.; Smith, M. R., III. *Science* **2002**, *295*, 305-308. d) Ishiyama, T.; Takagi, J.; Ishida, K.; Miyaura, N.; Anastasi, N. R.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 390-391. e) Coventry, D. N.; Batsanov, A. S.; Goeta, A. E.; Howard, J. A. K.; Marder, T. B.; Perutz, R. N. *Chem. Commun.* **2005**, 2172-2174. f) Kawamorita, S.; Ohmiya, H.; Hará, K.; Fukuoka, A.; Sawamura, M. *J. Am. Chem. Soc*. **2009**, *131*, 5058-5059. g) Ros, A.; Estepa, B.; Lopez-Rodriguez, R.; Alvarez, E.; Fernandez, R.; Lassaletta, J. M. *Angew. Chem. Int. Ed.* **2011**, *50*, 11724 -11728. h) Roosen, P. C.; Kallepalli, V. A.; Chattopadhyay, B.; Singleton, D. A.; Maleczka, R. E. Jr.; Smith III, M. R. *J. Am. Chem. Soc*. **2012**, *134*, 11350-11353. i) Crawford, K. M.; Ramseyer, T. R.; Daley, C. J. A.; Clark, T. B. *Angew. Chem. Int. Ed.* **2014**, *53*, 7589-7593. j) Kuninobu, Y.; Ida, H.; Nishi, M.; Kanai, M. *Nat. Chem.* **2015**, *7*, 712–717. k) Bisht, R.; Chattopadhyay, B. *J. Am. Chem. Soc.* **2016**, *138*, 84-87. l) Wang, G.; Liu, L.; Ding, Y. S.; Zhou, J.; Mao, S.; Li, P. *J. Am. Chem. Soc.* **2017**, **139**, 91-94. m) Li, H. L.; Kuninobu, Y.; Kanai, M. *Angew. Chem. Int. Ed.* **2017**, *56*, 1495- 1499. n) Su, B.; Hartwig, J. F. *Angew. Chem. Int. Ed*. **2018**, *57*, 10163-10167.

[39] a) Liu, X. W.; Echavarren, J.; Zarate, C.; Martin, R. *J. Am. Chem. Soc*. **2015**, *137*, 12470-12473. b) Zhang, J.; Dai, W.; Liu, Q.; Cao, S. *Org. Lett.* **2017**, *19*, 3283−3286. c) Niwa, T.; Ochiai, H.; Hosoya, T. *ACS Catal.* **2017**, *7*, 4535−4541. d) Sakaguchi, H.; Uetake, Y.; Ohashi, M.; Niwa, T.; Ogoshi, S.; Hosoya, T. *J. Am. Chem. Soc.* **2017**, *139*, 12855-12862. e) Tian, Y. M.; Guo, X. N.; Kuntze-Fechner, M. W.; Krummenacher, I.; Braunschweig, H.; Radius, U.; Steffen, A.; Marder, T. B. *J. Am. Chem. Soc.* **2018**, *140*, 17612-17623.

[40] a) Kinuta, H.; Tobisu, M.; Chatani, N. *J. Am. Chem. Soc.* **2015**, *137*, 1593-1600. b) Zarate, C.; Manzano, R.; Martin, R. *J. Am. Chem. Soc.* **2015**, *137*, 6754-6757. c) Mao, L.; Szabó, K. J.; Marder, T. B. *Org. Lett.* **2017**, *19*, 1204-1207.



Scheme 2-4: C-H, C-F and C-OMe borylations.

More recently, different methodologies have emerged to introduce boronic ester moieties without the use of any metals, simply using a catalytic amount of base (**Figure *2-5***).[41]

[41] a) Cid, J.; Gulyas, H.; Carbo, J. J.; Fernandez, E. *Chem. Soc. Rev.* **2012**, *41*, 3558-3570. b) Cuenca, A. B.; Shishido, R.; Ito, H.; Fernandez, E. *Chem. Soc. Rev.* **2017**, *46*, 415-430.

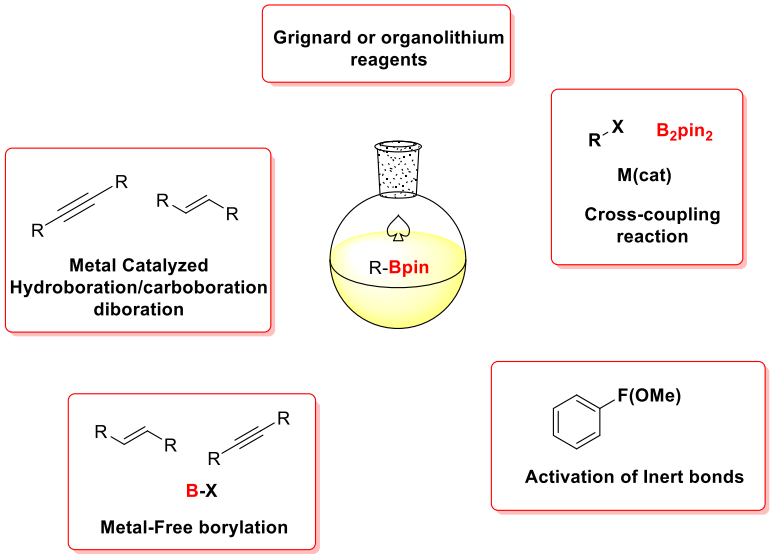
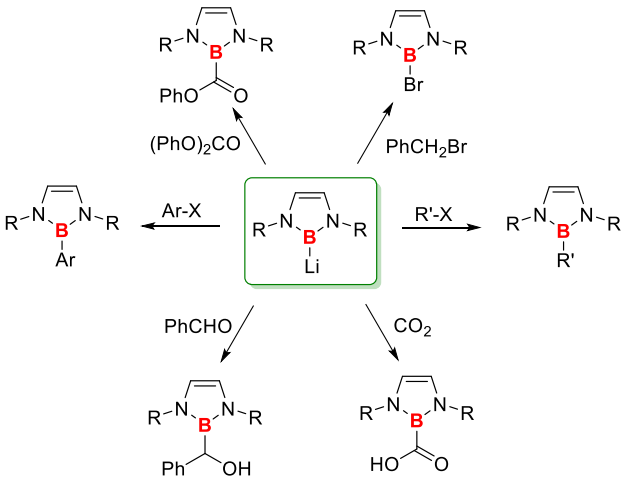


Figure 2-5: Different strategies for the synthesis of boronic esters.

Despite the large number of existing methodologies for the synthesis of boronic esters, most of them are based in the electrophilic nature of the boron atom. Nonetheless, in 2006, Segawa, Yamashita and Nozaki discovered that there are some boryl complexes that could act as nucleophiles. They succeeded in the synthesis, isolation and characterization by X-Ray crystallography of the first boryl lithium compound. Moreover, they also studied its reactivity in the presence of a variety of electrophiles. The results demonstrated that this boryl complex is indeed a strong nucleophile and opened a new window in boron organic chemistry. However, despite the breakthrough, the synthetic application of the boryl lithium species has been hampered by their instability (**Scheme *2-5***).[42] Following these investigations, the group of Nozaki, and later

[42] a) Segawa, Y.; Yamashita, M.; Nozaki, K. *Science* **2006**, *314*, 113-115. b) Marder, T. B. *Science* **2006**, *314*, 69-70. c) Braunschweig, H. *Angew. Chem. Int. Ed.* **2007**, *46*, 1946-1948. d) Segawa, Y.; Suzuki, Y.; Yamashita, M.; Nozaki, K. *J. Am. Chem. Soc.* **2008**, *130*, 16069- 16079. e) For a more theoretical study, see: Cheung, M. S.; Marder, T. B.; Lin, Z. *Organometallics* **2011**, *30*, 3018-3028.

Weetman, were able to transform this boryl lithium reagent into boryl magnesium compounds, increasing the stability by treating it with magnesium bromide.[43]



Scheme 2-5: Reactivity of boryl lithium compounds.

Nucleophilic boron species opened a completely new pathway to the formation of carbon-boron bonds.[44] Several methodologies have been published to generate nucleophilic boron species,[45] but among them,

[43] a) Yamashita, M.; Suzuki, Y.; Segawa, Y.; Nozaki K. *J. Am. Chem. Soc*. **2007**, *129*, 9570-9571. b) Pécharman, A. -F.; Colebatch, A. L.; Hill, M. S.; McMullin, C. L.; Mahon, M. F.; Weetman, C. *Nature Commun.* **2017**, *8*, 15022-15029.

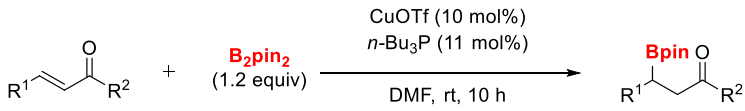
[44] a) Dang, L.; Lin, Z.; Marder, T. B. *Chem. Commun*. **2009**, 3987-3995; b) Cid, J.; Gulyás, H.; Carbó, J. J.; Fernández, E. *Chem. Soc. Rev*. **2012**, *41*, 3558-3570; c) Yamashita, M.; Nozaki K. Boryl Anions. In *Synthesis and Application of Organoboron Compounds;* Fernández, E., Whiting, A. Ed.; Springer International Publishing: Switzerland, **2015**; pp 1-38.

[45] a) Lee, K. S.; Zhugralin, A. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2009**, *131*, 7253-7255. b) Bonet, A.; Gulyás, H.; Fernández, E. *Angew. Chem. Int. Ed.* **2010**, *49*, 5130-5134. c) Bonet, A.; Pubill-Ulldemolins, C.; Bo, C.; Gulyás, H.; Fernández, E. Angew. *Chem. Int. Ed.* **2011**, *50*, 7158-7161. d) Wu, H.; Radomkit, S.; O'Brien, J. M.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2012**, *134*, 8277-8285. e) Kleeberg, C.; Crawford, A. G.; Batsanov, A. S.; Hodgkinson, P.; Apperley, D. C.; Cheung, M. S.; Lin, Z.; Marder, T. B. *J. Org. Chem*. **2013**, *77*, 785-789. f) Sanz, X.; Lee, G. M.; Pubill-Ulldemolins, C.; Bonet, A.; Westcott, S. A.;

copper-catalyzed borylations have proven to be the most versatile and will be discussed in the next section.

2.1.3. Copper-Catalyzed Borylations.

It was 2000, when Hosomi reported the copper-catalyzed hydroboration of α,β-unsaturated ketones with B_2pin_2.[46] This breakthrough discovery led to a completely new area of research in organometallic chemistry. It was at this point when the catalytic activity of copper(I) salts was disclosed and how the addition of phosphines dramatically improved the results. The outcome of the reaction was even better than the one obtained with more expensive transition metals, such as platinum or rhodium. The use of copper allowed for the reaction to take place at room temperature. They tested the methodology with different enones, and they successfully converted the products into the correspondent β-hydroxy ketones by means of a simple oxidation (**Scheme *2-6***).



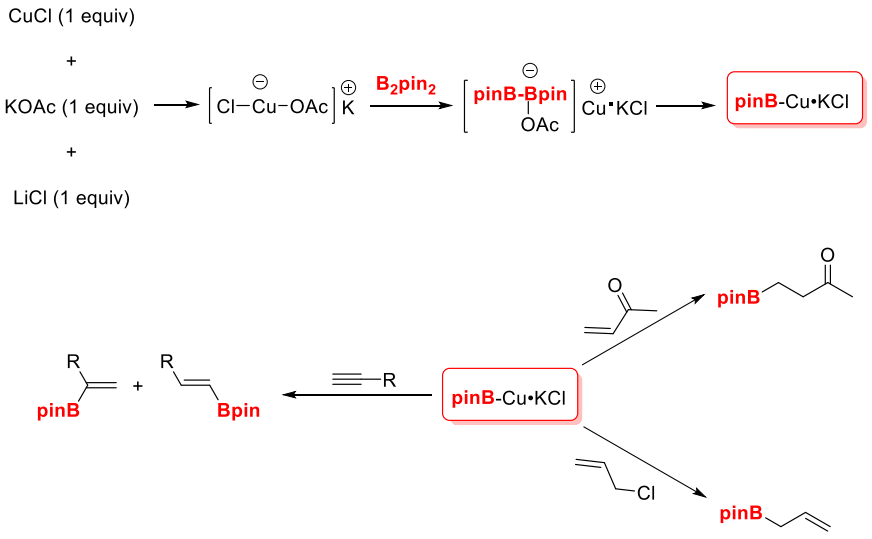
Scheme 2-6: Copper-catalyzed borylation by Hosomi.

Following the work of Hosomi, Professor Miyaura reported the hydroboration of different unsaturated compounds using copper(I) chloride, lithium chloride and potassium acetate as base. Mixing these reagents with B_2pin_2, provoked the B-B bond cleavage and the *in situ* formation of copper-boryl species, which could undergo β-borylation of α,β-unsaturated

Gulyás, H.; Bo, C.; Fernández, E. *Org. Biomol. Chem.* **2013**, *11*, 7004-7010. g) Cuenca, A. B.; Shishido, R.; Ito, H.; Fernández, H. *Chem. Soc. Rev.* **2017**, *46*, 415-430.

[46] Ito, H.; Yamanaka, H.; Tateiwa, J.; Hosomi, A. *Tetrahedron Lett.* **2000**, *41*, 6821-6825.

carbonyl compounds, hydroboration of alkynes and allylic substitution (**Scheme *2-7***).[47] They proposed that the reaction between CuCl and KOAc in the presence of LiCl generate the active specie [CuClOAc]K. After transmetalation with the diboron compound, the copper-boryl nucleophile is generated.



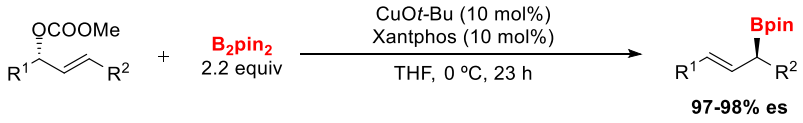
Scheme 2-7: Copper-catalyzed borylation by Miyaura.

While both reports used slightly different conditions, they agreed that copper-boryl complexes are formed *in situ*, and that these complexes behaved as formal boron nucleophiles.

It was also in Japan, when five years later Sawamura published the stereospecific copper-catalyzed borylation of allylic carbonates. With this contribution, the potential of copper-catalyzed borylations was revealed.[48]

[47] a) Takahashi, K.; Ishiyama, T.; Miyaura, N. *Chem. Lett.* **2000**, *29*, 982-983. b) Takahashi, K.; Ishiyama, T.; Miyaura, N. *J. Organomet. Chem.* **2001**, *625*, 47-53.
[48] Ito, H.; Kawakami, C.; Sawamura, M. *J. Am. Chem. Soc.* **2005**, *127*, 16034-16035.

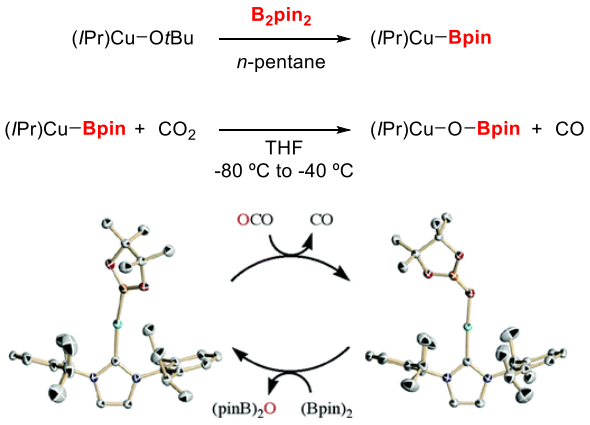
They proposed that the *in situ* formed boryl-complex catalyzed the S_N2' borylation of allylic carbonates, affording allylboron compounds via a γ-selective and stereospecific substitution reaction. This methodology yielded enantiomerically enriched allyl boronates with excellent results (**Scheme *2-8***).



Scheme 2-8: Copper-catalyzed borylation of allylic carbonates by Sawamura.

At the same time, Sadighi reported the copper-catalyzed reduction of CO_2 to CO by B_2pin_2. They also reported the isolation and X-Ray characterization of copper(I) boryl complex [(*IPr*)Cu-Bpin], the reductant of the reaction, and the resulting borate complex [(*IPr*)Cu(OBpin)] formed after deoxygenation of carbon dioxide. The copper-boryl complex could be regenerated by reaction of the borate with the diboron compound forming the stable product pinB-O-Bpin (**Scheme *2-9***).[49] Later, the same authors reported the reduction of aldehydes through a 1,2-diboration.[50]

[49] Laitar, D. S.; Mueller, P.; Sadighi, J. P. *J. Am. Chem. Soc.* **2005**, *127*, 17196-17197.
[50] Laitar, D. S.; Tsui, E. Y.; Sadighi, J. P. *J. Am. Chem. Soc.* **2006**, *128*, 11036-11037.

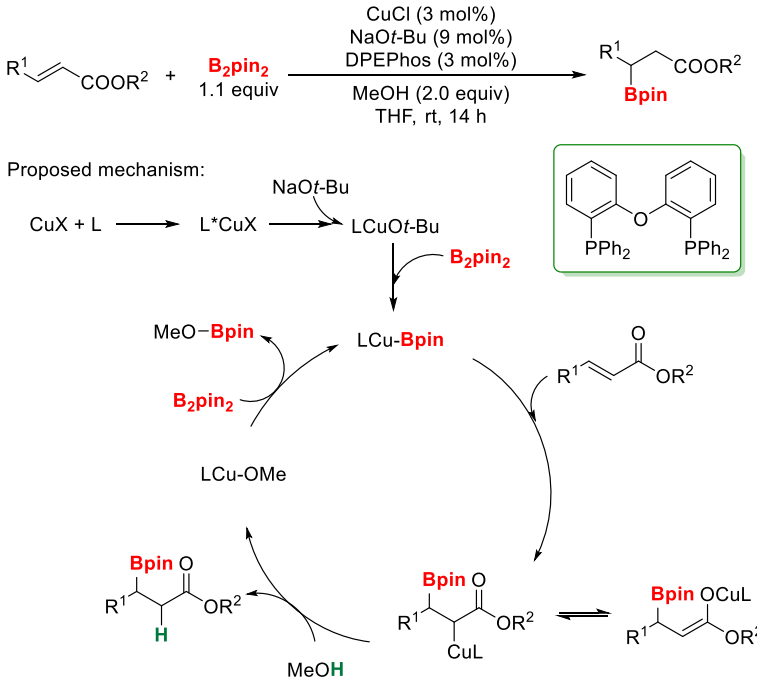


Scheme 2-9: Reduction of CO_2 and X-Ray images of both the copper-boryl complex and the borate-copper complex.

After these two publications, an important contribution was reported by Yun for the copper-catalyzed borylation of α,β-unsaturated carbonyl compounds with B_2pin_2 (**Scheme *2-10***).[51] In this work, there were two important discoveries that were crucial in the subsequent development of the field. First, Yun reported the importance of using alcohols in the reaction to improve the rate of the reaction. The reason behind this is that after the insertion step, the formation of copper methoxide is needed to regenerate the catalytic cycle from the recently formed copper enolate. Without a proton source, this transformation is really slow. Therefore, methanol protonates the copper enolate, forming copper methoxide, which can start again the catalytic cycle. Previously, Sawamura and Sadighi used highly sensitive CuO*t*-Bu and, therefore, the use of a glovebox was necessary. However, Yun demonstrated that the *in situ* formation of the copper alkoxide by reaction of copper(I) chloride and sodium *tert*-butoxide

[51] Mun, S.; Lee, J. E.; Yun, J. *Org. Lett.* **2006**, *8*, 4887-4889.

worked equally well, making the experimental process easier and more convenient.



Scheme 2-10: Borylation of α,β-unsaturated carbonyl compounds by Yun.

In the last fifteen years, the number of publications on copper-catalyzed borylation reactions have exponentially increased. Many groups around the globe have successfully demonstrated that most of the organocopper chemistry known to form carbon-carbon bonds, can now be applied to the formation of carbon-boron bonds (**Scheme *2-11***). Nucleophilic copper-boryl complex can react with a broad variety of electrophiles such as

aldehydes,[52] imines,[53] α,β-unsaturated compounds,[54] alkynes,[55] alkenes and allenes.[56] A comprehensive review of the literature exceeds the scope of the introduction of this chapter. Therefore, only selective examples about copper-catalyzed borylations of non-polarized alkenes will be included in the next sections.

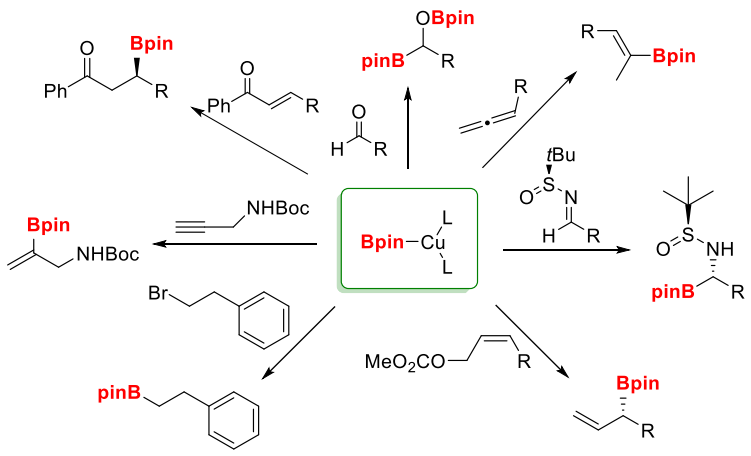
[52] For selected examples see: a) Molander, G. A.; Wisniewski, S. R. *J. Am. Chem. Soc*. **2012**, *134*, 16856-16868. b) Kubota, K.; Yamamoto, E.; Ito, H. *J. Am. Chem. Soc*. **2015**, *137*, 420-424. c) Wang, L.; Zhang, T.; Sun, W.; He, Z.; Xia, C.; Lan, Y.; Liu, C. *J. Am. Chem. Soc.* **2017**, *139*, 5257-5264. d) Tagichi, J.; Takeuchi, T.; Takahashi, R.; Masero, F.; Ito, H. *Angew. Chem. Int. Ed.* **2019**, *58*, 7299-7303.

[53] For selected examples see: a) Beenen, M. A.; An, C.; Ellman, J. A. *J. Am. Chem. Soc.* **2008**, *130*, 6910-6911. b) Hong, K.; Morken, J. P. *J. Am. Chem. Soc.* **2013**, *135*, 9252-9254. c) Wang, D.; Cao, P.; Wang, B.; Jia, T.; Lou, Y.; Wang, M.; Liao, J. *Org. Lett.* **2015**, *17*, 2420-2423. d) Li, Z.; Zhang, L.; Nishiura, M.; Hou, Z. *ACS Catal*. **2019**, *9*, 4388-4393.

[54] For selected examples see: a) Lee, J. E.; Yun, J. *Angew. Chem. Int. Ed*. **2008**, *47*, 145-147. b) Lillo, V.; Prieto, A.; Bonet, A.; Díaz-Requejo, M. M.; Ramıírez, J.; Pérez, P. J.; Fernández, E. *Organometallics* **2009**, *28*, 659-662. c) Chen, I. H.; Yin, L.; Itano, W.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc*. **2009**, *131*, 11664-11665. e) O'Brien, J. M; Lee, K. S.; Hoveyda, A. H. *J. Am. Chem. Soc*. **2010**, *132*, 10630-10633. f) Chen, I. H.; Kanai, M.; Shibasaki, M. *Org. Lett.* **2010**, *12*, 4098-4101. g) Moure, A. L.; Gomez-Arrayas, R.; Carretero, J. C. *Chem. Commun*. **2011**, *47*, 6701-6703.

[55] For selected examples see: a) Lee, J. -E.; Kwon, J.; Yun, J. *Chem. Commun*. **2008**, 733-734. b) Jang, H.; Zhugralin, A. R.; Lee, Y.; Hoveyda, A. H.; *J. Am. Chem. Soc.* **2011**, *133*, 7859-7871. c) Moure, A. L.; Arrayás, R. G.; Cárdenas, D. J.; Alonso, I.; Carretero, J. C. *J. Am. Chem. Soc*. **2012**, *134*, 7219-7222. d) Moure, A. L.; Mauleón, P.; Arrayás, R. G.; Carretero, J. C. *Org. Lett.* **2013**, *15*, 2054-2057. e) Moon, J. H.; Jung, H. -Y.; Lee, Y. J.; Lee, S. W.; Yun, J.; Lee, J. Y. *Organometallics* **2015**, *34*, 2151-2159. f) Kojima, C.; Lee, K. H.; Lin, Z.; Yamashita, M. *J. Am. Chem. Soc.* **2016**, *138*, 6662-6669. For carboboration of alkynes, see: Alfaro, R.; Parra, A.; Aleman, J.; García-Ruano, J. L.; Tortosa, M. *J. Am. Chem Soc.* **2012**, *134*, 15165-15168.

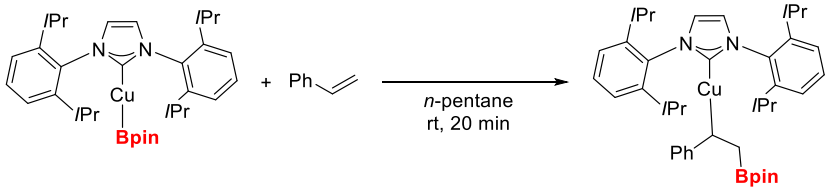
[56] For selected examples see: a) Yuan, W.; Ma, S. *Adv. Synth. Catal*. **2012**, *354*, 1867-1872. b) Meng, F.; Jung, B.; Haeffner, F.; Hoveyda, A. H. *Org. Lett.* **2013**, *15*, 1414-1417. c) Semba, K.; Shinomiya, M.; Fujihara, T.; Terao, J.; Tsuji, Y. *Chem. Eur. J*. **2013**, *19*, 7125-7132. d) Semba, K.; Fujihara, T.; Terao, J.; Tsuji, Y. *Angew. Chem. Int. Ed*. **2013**, *52*, 12400-12403. e) Yuan, W.; Zhang, X.; Yu, Y.; Ma, S. *Chem. Eur. J*. **2013**, *19*, 7193-7202. f) Meng, F. K.; Jang, H.; Jung, B.; Hoveyda, A. H. *Angew. Chem. Int. Ed*. **2013**, *52*, 5046-5051. g) Jang, H.; Jung, B.; Hoveyda, A. H. *Org. Lett*. **2014**, *16*, 4658-4661. h) Yuan, W.; Song, L.; Ma, S. *Angew. Chem. Int. Ed*. **2016**, *55*, 3140-3143.



Scheme 2-11: Copper-boryl complex as tool in organic synthesis.

2.1.3.1. Copper-Catalyzed Borylation of Non-Polarized Alkenes.

Sadighi's group isolated, in 2006, the complex formed after the insertion of the double bound of styrene into a (NHC)-copper-boryl complex (**Scheme *2-12***). This insertion is highly regioselective, however, this complex could be rearranged to the other regioisomer upon heating (elimination/reinsertion).[57]



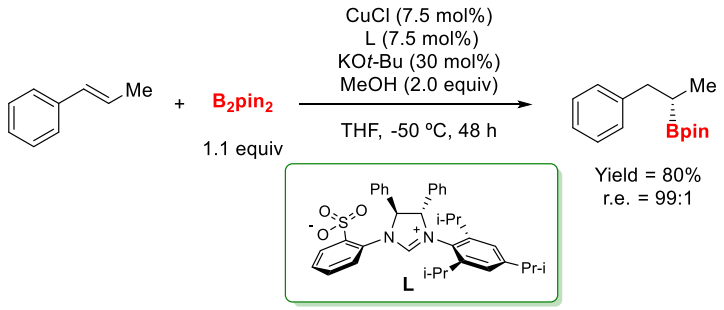
Scheme 2-12: Insertion of an alkene into a copper-boron bond.

One year later, Marder and coworkers, reported a computational study about the insertion reaction of alkenes into copper-boryl(I) complexes. DFT

[57] Laitar, D. S.; Tsui, E. Y.; Sadighi, J. P. *Organometallics* **2006**, *25*, 2405-2408.

calculations supported that this insertion implies a nucleophilic attack of copper-boryl species to the alkene.[58]

In 2009, Hoveyda's group reported that enantiomerically pure (NHC)-copper(I) complexes were able to catalyzed the borylation reaction of styrenes not only with complete regioselectivity, as reported by Sadighi, but also with excellent enantioselectivities (**Scheme *2-13***).[59] Some years later, the same group reported the hydroboration of vinylsilanes to obtain enantiomerically enriched borosilanes.[60]

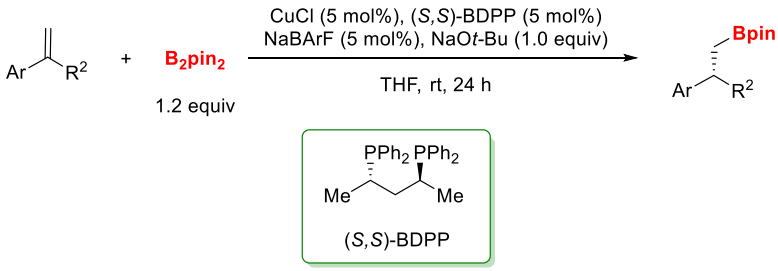


Scheme 2-13: Copper(I) Catalyzed Asymmetric Hydroboration.

Similar studies were carried out by the group of Xiong. They reported an asymmetric formal hydroboration of α,α-diaryl substituted alkenes and α-alkyl styrenes in excellent yields and enantiomeric excesses (**Scheme *2-14***).[61] More recently, Hong and Meng published the same reaction with

[58] Dang, L.; Zhao, H.; Lin, Z.; Marder, T. B. *Organometallics* **2007**, *26*, 2824-2832.
[59] a) Lee, Y.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2009**, *131*, 3160-3161. b) Corberán, R.; Mszar, N. W.; Hoveyda, A. H. *Angew. Chem. Int. Ed.* **2011**, *50*, 7079-7082.
[60] Meng, F. K.; Jang, H. J.; Hoveyda, A. H. *Chem. Eur. J.* **2013**, *19*, 3204-3214.
[61] Wang, Z.; He, X.; Zhang, R.; Zhang, G.; Xu, G.; Zhang, Q.; Xiong, T.; Zhang, Q. *Org. Lett.* **2017**, *19*, 3067-3070.

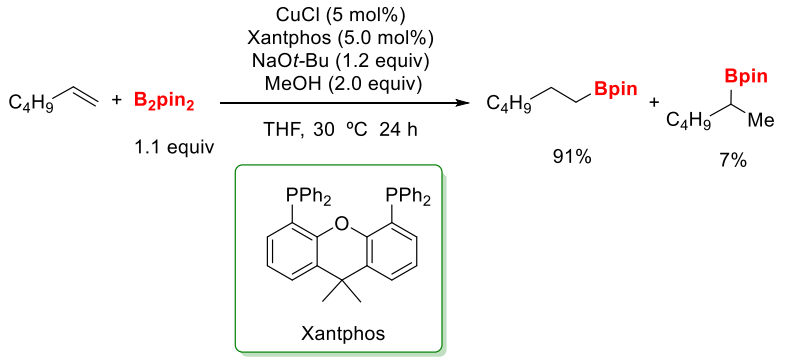
comparable result, however they provided some insight into the stereodetermining step through DFT calculations.[62]



Scheme 2-14: Copper(I) catalyzed asymmetric hydroboration of α,α-disubstituted alkenes.

Ito and coworkers were the first to show that the borylation of alkyl substituted alkenes was also possible (**Scheme *2-15***).[63] The reaction is highly regioselective towards the anti-Markovnikov product and they concluded that the nature of the ligand played a crucial role in the observed regioselectivity. They applied this new methodology to the *exo*-cyclization of alkenyl halides, running the reaction in the absence of methanol.[64]

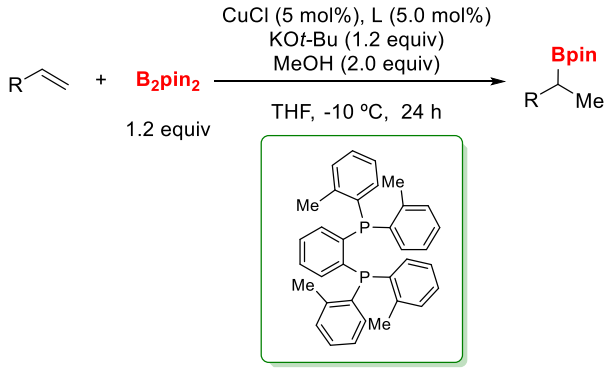
[62] Wen, L.; Cheng, F.; Li, H.; Zhang, S.; Hong, X.; Meng, F. *Asian J. Org. Chem.* **2018**, *7*, 103-106.
[63] Kubota, K.; Yamamoto, E.; Ito, H. *J. Am. Chem. Soc.* **2013**, *135*, 2635−2640.
[64] a) Kubota, K.; Yamamoto, E.; Ito, H. *J. Am. Chem. Soc*. **2013**, *135*, 2635-2640. b) Yamamoto, E.; Kojima, R.; Ito, H. *Synlett* **2016**, *27*, 272-276. c) Kubota, K.; Iwamoto, H.; Ito, H. *Org. Biomol. Chem*. **2017**, *15*, 285-300.



Scheme 2-15: Anti-Markovnikov hydroboration of alkyl-substituted alkenes.

Ito demonstrated later how important the election of the ligand was, publishing the Markovnikov copper-catalyzed borylation of alkyl substituted alkenes (**Scheme *2-16***).[65] Both methodologies together are two complementary approaches to these alkenyl boronates.

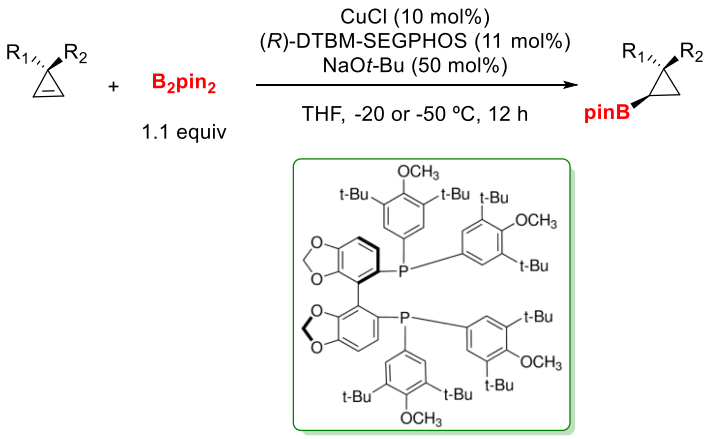
[65] Iwamoto, H.; Kubota, K.; Ito, H. *Chem. Commun.* **2016**, *52*, 5916-5919.



Scheme 2-16: Markovnikov Hydroboration of Alkyl-Substituted Alkenes.

More related to the present chapter is the copper-catalyzed borylation of strained alkenes. Tortosa and coworkers reported, in 2014, the synthesis of enantioenriched cyclopropylboronates through a copper-catalyzed desymmetrization of cyclopropenes (**Scheme *2-17***).[66] In order to obtain high levels of stereoselectivities, a bulky bidentate phosphine ligand was required. This ligand also played a key role avoiding the cyclopropane dimerization. At the same time, Lin and coworkers reported the same transformation. They use a different ligand but, to achieve high levels of stereocontrol, an ester moiety was needed in the cyclopropene.[67]

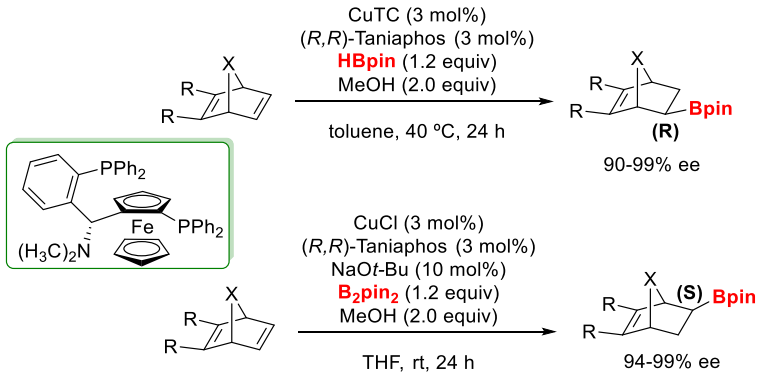
[66] Parra, A.; Amenos, L.; Guisan-Ceinos, M.; Lopez, A.; Garcia-Ruano, J. L.; Tortosa, M. *J. Am. Chem. Soc*. **2014**, *136*, 15833-15836.
[67] Tian, B.; Liu, Q.; Tong, X.; Lin, G. Q. *Org. Chem. Front.* **2014**, *1*, 1116-1122.



Scheme 2-17: Enantioselective desymmetrization of cyclopropenes.

In 2015, Yun and coworkers introduced the enantiodivergent borylation of strained bicyclic olefins.[68] They obtained high levels of stereocontrol using the bidentate phosphine (*R*,*R*)-Taniaphos. They succeeded in obtaining both possible enantiomers by simply tuning the boron source from B_2pin_2 to HBpin (**Scheme *2-18***). In the same year, Tortosa and coworkers studied the relative reactivity of different strained alkenes in copper-catalyzed borylations.[69]

[68] Lee, H.; Lee, B. Y.; Yun, J. *Org. Lett.* **2015**, *17*, 764-766.
[69] Parra, A.; López, A.; Díaz-Tendero, S.; Amenós, L.; Garcia-Ruano, J. L.; Tortosa, M. *Synlett* **2015**, *26*, 494-500.



Scheme 2-18: Enantioselective hydroboration of strained alkenes.

The results regarding copper-catalyzed borylation of cyclobutenes will be explained in the following pages of this chapter.[70]

2.1.4. Importance of Cyclobutanes in Organic Chemistry.

Small and strained molecules have attracted the interest of chemists throughout history. If we compare cyclopropane and its homologue the cyclobutane, the former has drawn much more interest than the latter. Cyclopropane ring have a strain energy of 27.5 Kcal/mol, while the cyclobutane ring have 26.7 Kcal/mol. Both rings have almost the same strain energy. When strain energies are calculated, you can dissect the result between C-C and C-H contributions. While the C-C energy in cyclopropanes is 10 Kcal/mol higher, this is compensated by the difference in C-H energy (8 Kcal/mol).[71] Cyclobutanes are present in both synthetic and natural products. Among the most well-known cyclobutane containing molecules we have cubane, a non-natural high strained molecule.[72] But not

[70] Guisan-Ceinos, M.; Parra, A.; Martin-Heras, V.; Tortosa, M. *Angew. Chem. Int. Ed.* **2016**, *55*, 6969-6972.
[71] Khoury, P. R.; Goddard, J. D.; Tam, W. *Tetrahedron* **2004**, *60*, 8103-8112.
[72] Eaton, P. E.; Cole, T. W. *J. Am. Chem. Soc.* **1964**, *86*, 962–964.

only synthetic molecules contain cyclobutanes in its structure. A wide number of natural products have this peculiar moiety in their framework. We can find it in simple terpenes as α-pinene or the sex attractant pheromone grandisol. But also, this structure exists in more complex molecules such as (-)-Bielschowskysin or Penitrem A (**Figure *2-6***).[73]

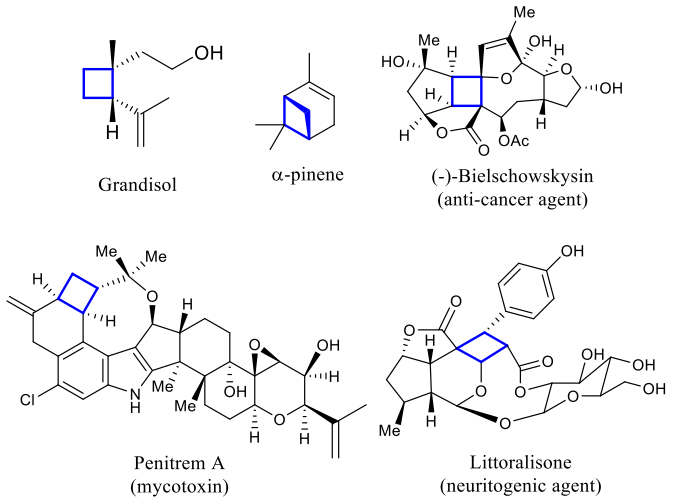
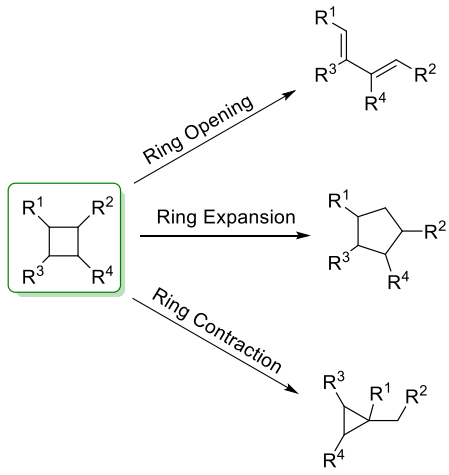


Figure 2-6: Cyclobutane containing molecules.

[73] For some examples of natural products and pharmaceuticals containing cyclobutanes, see a) Hansen, T. V., Stenstrom, Y. (**2001**) *Naturally occurring cyclobutanes. Organic Synthesis: Theory and Applications*, Volume 5, 1-38. b) Sinninghe Damste, J. S.; Strous, M.; Rijpstra, W. I. C.; Hopmans, E. C.; Geenevasen, J. A. J.; van Duin, A. C. T.; van Niftrik, L. A.; Jetten, M. S. M.; *Nature* **2002**, *419*, 708-712. c) Vilaine, J. P.; Thollon, C.; Villeneuve, N.; Peglion, J. L. *Eur. Heart J. Suppl.* **2003**, *5*, G26. c) Mascitti, V.; Corey, E. J. *J. Am. Chem. Soc.* **2006**, *128*, 3118-3119. d) Nouri, D. H.; Tantillo, D. J. *Curr. Org. Chem.* **2006**, *10*, 2055-2074. e) Dembitsky, V. M. *J. Nat. Med.* **2008**, **62**, 1-33. f) Sergeiko, A.; Poroikov, V. V.; Hanus, L. O.; Dembitsky, V. M. *Open Med. Chem. J.* **2008**, *2*, 26-37. g) Blakemore, D. C.; Bryans, J. S.; Carnell, P.; Carr, C. L.; Chessum, N. E. A.; Field, M. J.; Kinsella, N.; Osborne, S. A.; Warren, A. N.; Williams, S. C. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 461-464. h) Cipres, A.; O'Malley, D. P.; Li, K.; Finlay, D.; Baran, P. S.; Vuori, K. *ACS Chem. Biol.* **2010**, *5*, 195. i) Bach, T.; Hehn, J. P. *Angew. Chem. Int. Ed.* **2011**, *50*, 1000-1045. j) Mercer, J. A. M.; Cohen, C. M.; Shuken, S. R.; Wagner, A. M.; Smith, M. W.; Moss III, F. R.; Smith, M. D. Vahala, R.; Gonzalez-Martinez, A.; Boxer, S. G.; Burns. N. Z. *J. Am. Chem. Soc.* **2016**, *138*, 15845-15848.

Furthermore, cyclobutanes have proved to be valuable synthetic intermediates for several transformations. Due to the strain energy in the ring (25.6 kcal/mol), cyclobutanes are prone to ring-opening reaction as well as ring expansions. Also, they can be used to synthetize cyclopropanes through ring-contraction reactions (**Scheme *2-19***).[74] Therefore, the preparation of this strained cycles has become a really active area.[75] They provide unique rigidity and three dimensionality which could be crucial in drug discovery.[76]



Scheme 2-19: Applications of cyclobutanes.

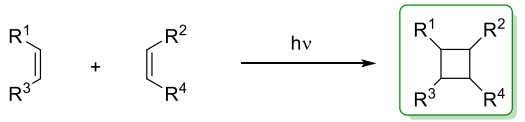
[74] a) Namyslo, J. C.; Kaufmann, D. E. *Chem. Rev.* **2003**, *103*, 1485-1537. b) Hoffmann, N. *Chem. Rev.* **2008**, *108*, 1052-1103. c) Seiser, T.; Saget, T.; Tran, D. N.; Cramer, N. *Angew. Chem. Int. Ed.* **2011**, *50*, 7740-7752.

[75] For some reviews on synthesis of cyclobutanes, see a) Lee-Ruff, E.; Mladenova, G. *Chem. Rev.* **2003**, *103*, 1449-1483. b) Yoon, T. P. *ACS Catal.* **2013**, *3*, 895-902. c) Poplata, S.; Tröster, A.; Zou, Y. -Q.; Bach, T. *Chem. Rev.* **2016**, *116*, 9748-9815.

[76] a) Ruzyllo, W.; Tendera, M.; Ford, I.; Fox, K. M. *Drugs* **2007**, *67*, 393-405. b) Carreira, E. M.; Fessard, T. C. *Chem. Rev.* **2014**, 114, 8257-8322.

2.1.5. Synthesis of Cyclobutanes.

Among the classical methodologies to prepare chiral cyclobutanes stands out the [2+2] cycloadditions (**Scheme *2-20***).[77] In this reaction, two double bonds reacts in a photochemical electrocyclic reaction to form a cyclobutane.

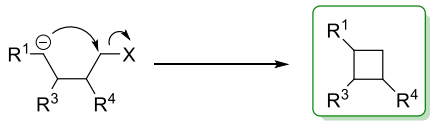


Scheme 2-20: [2+2] cycloaddition reaction to form cyclobutanes.

Another known methodology is the acyclic ring closure (**Scheme *2-21***).[78] This included the 1,4-cyclization reaction of functionalized alkyl halides or pseudohalides.

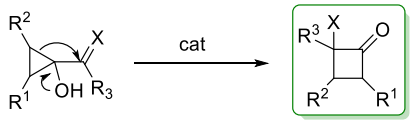
[77] Recent selected work on [2+2] cycloadditions for the synthesis of cyclobutanes: a) Zhu, M.; Zheng, C.; Zhang, X.; You, S. -L. *J. Am. Chem. Soc.* **2019**, *141*, 2636-2644. b) Wiest, J. M.; Conner, M. L.; Brown, M. K. *J. Am. Chem. Soc.* **2018**, *140*, 15943-15949. c) Poplata, S.; Bach, T. *J. Am. Chem. Soc.* **2018**, *140*, 3228−3231. d) Kramm, F.; Teske, J.; Ullwer, F.; Frey, W.; Plietker, B. *Angew. Chem. Int. Ed.* **2018**, *57*, 13335-13338. e) Zhou, C.; Lei, T.; Wei, X. Z.; Liu, Z.; Chen, B.; Ramamurthy, V.; Tung, C. H.; Wu, L. Z. *Org. Lett.* **2018**, *20*, 6808−6811. f) Conner, M. L.; Xu, Y.; Brown, M. K. *J. Am. Chem. Soc.* **2015**, *137*, 3482−3485. g) Du, J.; Skubi, K. L.; Schultz, D. M.; Yoon, T. P. *Science* **2014**, *344*, 392-396.

[78] a) Shu, C.; Noble, A.; Aggarwal, V. K. *Angew. Chem. Int. Ed.* **2019**, *58*, 3870-3874. b) Hazra, C. K.; Jeong, J.; Kim, H.; Baik, M. -H.; Park, S.; Chang, S. *Angew. Chem. Int. Ed.* **2018**, *57*, 2692-2696. c) Wang, Y. M.; Bruno, N. C.; Placeres, A. L.; Zhu, S.; Buchwald, S. L. *J. Am. Chem. Soc.* **2015**, *137*, 10524-10527. d) Johnson, T.; Choo, K. L.; Lautens, M. *Chem. Eur. J.* **2014**, *20*, 14194-14197. e) Panish, R.; Chintala, S. R.; Boruta, D. T.; Fang, Y.; Taylor, M. T.; Fox, J. M. *J. Am. Chem. Soc.* **2013**, *135*, 9283-9286. f) Kubota, K.; Yamamoto, E.; Ito, H. *J. Am. Chem. Soc.* **2013**, *135*, 2635-2640.



Scheme 2-21: Acyclic ring closure to form cyclobutanes.

The catalytic Wagner–Meerwein shifts of cyclopropanols is a useful strategy for the synthesis of cyclobutanones (**Scheme *2-22***).[79] The reaction involves the 1,2-alkyl shift into an olefin moiety or carbonyl group to afford the corresponding cyclobutanone.

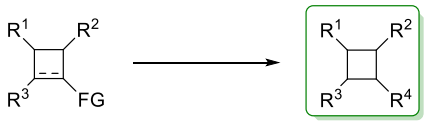


Scheme 2-22: Catalytic Wagner-Meerwein shift for the synthesis of cyclobutanones.

A straightforward strategy to prepare funtionalized cyclobutanes is the direct functionalization of cyclobutanes or cyclobutenes (**Scheme *2-23***).[80]

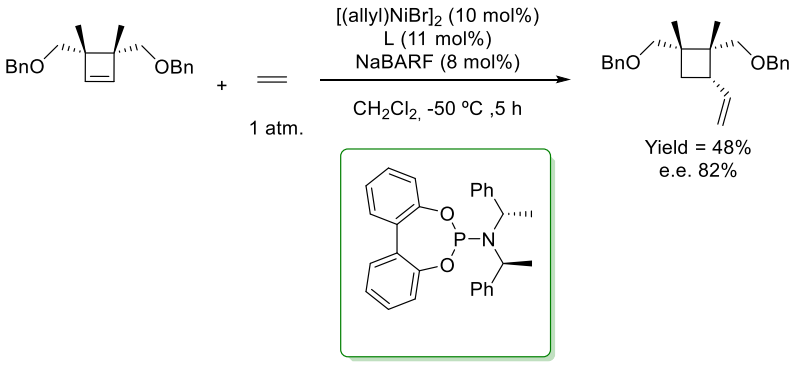
[79] a) Shim, S. Y.; Choi, Y.; Ryu, D. H. *J. Am. Chem. Soc.* **2018**, *140*, 11184-11188. b) Kleinbeck, F.; Toste, F. D. *J. Am. Chem. Soc.* **2009**, *131*, 9178-9179. c) Trost, B. M.; Yasukata, T. *J. Am. Chem. Soc.* **2001**, *123*, 7162-7163.

[80] a) Fawcett, A.; Biberger, T.; Aggarwal, V. K. *Nat. Chem.* **2019**, *11*, 117-122. b) Chen, Y. J.; Hu, T. J.; Feng, C. G.; Lin, G. Q. *Chem. Commun.* **2015**, *51*, 8773-8776. c) Xiao, K. J.; Lin, D. W.; Miura, M.; Zhu, R. Y.; Gong, W.; Wasa, M.; Yu, J. Q. *J. Am. Chem. Soc.* **2014**, *136*, 8138-8142. d) Aitken, D. J.; Caboni, P.; Eijsberg, H.; Frongia, A.; Guillot, R.; Ollivier, J.; Piras, P. P.; Secci, F. *Adv. Synth. Catal.* **2014**, *356*, 941-945. e) Reeves, C. M.; Eidamshaus, C.; Kim, J.; Stoltz, B. M. *Angew. Chem. Int. Ed.* **2013**, *52*, 6718-6721. f) Audisio, D.; Luparia, M.; Oliveira, M. T.; Klütt, D.; Maulide, N. *Angew. Chem. Int. Ed.* **2012**, *51*, 7314-7317.



Scheme 2-23: Direct functionalization of cyclobutanes and cyclobutenes.

Almost completely unexplored, there is a fifth strategy, the desymmetrization of *meso*-cyclobutenes. Regarding this strategy, at the time of this Doctoral Thesis, there was only one example of catalytic desymmetrization of *meso*-cyclobutenes. Rajanbabu and Liu, reported the enantioselective desymmetrization of strained alkenes catalyzed by nickel and a chiral phosphoramidite ligand. (**Scheme *2-24***).[81] In one of the examples, they succeeded in the enantioselective desymmetrization of a *meso*-cyclobutene with moderate yield and enantioselectivity.



Scheme 2-24: Hydrovinylation of *meso*-cyclobutenes.

[81] Liu, W.: Rajanbabu, T. V. *J. Org. Chem.* **2010**, *75*, 7636-7643.

2.1.6. Synthesis of Cyclobutylboronates.

Cyclobutanes with multiple stereocenters are important synthetic intermediates as mentioned above. In the context of the synthesis of functionalized cyclobutanes, cyclobutylboronates are promising synthetic intermediates due to the configurational stability of the C-B bond. The boryl moiety provides a handle for further functionalization through stereospecific transformations of the C-B bond (**Scheme *2-25***),[82] such as protodeborylation,[83] oxidation,[84] homologation,[85] Suzuki-Miyaura cross-coupling,[86] amination,[87] potassium trifluoroborates (Molander Salts)[88] or fluorination.[89] Therefore, different functionalized cyclobutanes can be envisioned from a common synthetic intermediate.

[82] a) *Boronic Acids: Preparation and Applications in Organic Synthesis and Medicine*; Hall, D., Ed.; Wiley-VCH: Weinheim, **2005**. b) Brown, H. C.; Basavaiah, D.; Kulkarni, S. U.; Bhat, N. G.; Vara Prasad, J. V. N. *J. Org. Chem.* **1988**, *53*, 239-246. c) Brown, H. C.; Singaram, B. *Acc. Chem. Res.* **1988**, *21*, 287-293. d) Matteson, D. S. *Chem. Rev.* **1989**, *89*, 1535-1551 e) Mlynarski, S. N.; Schuster, C. H.; Morken, J. P. *Nature* **2013**, *505*, 386-390. f) Neeve, E. C.; Geier, S. J.; Mkhalid, I. A. I.; Westcott, S. A.; Marder, T. B. *Chem. Rev.* **2016**, *116*, 9091.

[83] a) Zweifel, G.; Arzoumanian, H.; Whitney, C. C. *J. Am. Chem. Soc.* **1967**, *89*, 3652-3653. b) Roesner, S.; Blair, D. J.; Aggarwal, V. K. *Chem. Sci.* **2015**, *6*, 3718-3723. c) Cox, P. A.; Leach, A. G.; Campbell, A. D.; Lloyd-Jones, G. C. *J. Am. Chem. Soc.* **2016**, *138*, 9145-9157.

[84] a) Brown, H. C.; Zweifel, G. *J. Am. Chem. Soc.* **1959**, *81*, 247. b) Kabalka, G. W.; Shoup, T. M.; Goudagon, N. M. *J. Org. Chem*. **1989**, *54*, 5930-5933. c) Fang, L.; Yan, L.; Haeffner, F.; Morken, J. P. *J. Am. Chem. Soc.* **2016**, *138*, 2508-2511.

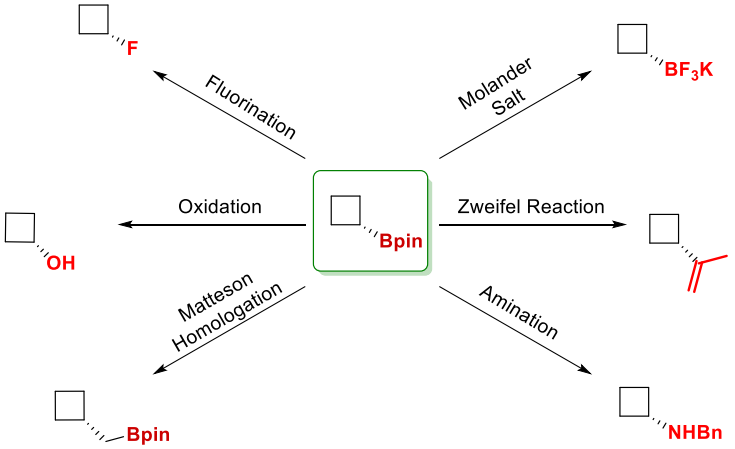
[85] a) Matteson, D. S.; Mah, R. W. H. *J. Am. Chem. Soc.* **1963**, *85*, 2599-2603. b) Matteson, D. S.; Majumdar, D. *J. Am. Chem. Soc.* **1980**, *102*, 7588-7590. c) Brown, H. C.; Singh, S. M.; Rangaishenvi, M. V. *J. Org. Chem.* **1986**, *51*, 3150-3155.

[86] a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457-2483. b) Kirchhoff, J. H.; Netherton, M. R.; Hills, I. D.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 13662-13663. c) Jana, R.; Pathak, T. P.; Sigman, M. S. *Chem. Rev.* **2011**, *111*, 1417-1492. d) Li, L.; Zhao, S.; Joshi-Pangu, A.; Diane, M.; Biscoe, M. R. *J. Am. Chem. Soc.* **2014**, *136*, 14027-14030.

[87] a) Hupe, E.; Marek, I.; Knochel, P. *Org. Lett.* **2002**, *4*, 2861-2863. b) Mlynarski, S. N.; Karns, A. S.; Morken, J. P. *J. Am. Chem. Soc.* **2012**, *134*, 16449-16451.

[88] a) Darses, S.; Genet, J. P. *Chem. Rev.* **2008**, *108*, 288-325. b) Sandrock, D. L.; Jean-Gerard, L.; Chen, C. Y.; Dreher, S. D.; Molander, G. A. *J. Am. Chem. Soc.* **2010**, *132*, 17108-17110. c) Lee, J. C. H.; McDonald, R.; Hall, D.G. *Nat. Chem.* **2011**, *3*, 894-899. d) Tellis, J. C.; Primer, D. N.; Molander, G. A. *Science* **2014**, *345*, 433-436.

[89] a) Furuya, T.; Ritter, T. *Org. Lett.* **2009**, *11*, 2860-2863. b) Li, Z.; Wang, Z.; Zhu, L.; Tan, X.; Li, C. *J. Am. Chem. Soc.* **2014**, *136*, 16439-16443.



Scheme 2-25: Versatility of the C-B bond in cyclobutylboronates.

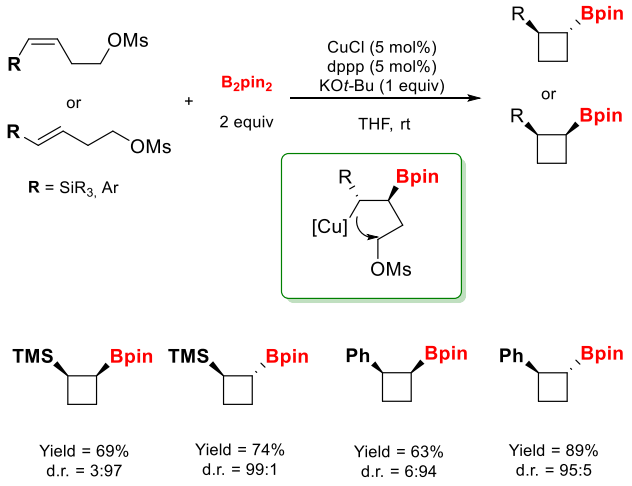
Despite their potential, the stereoselective synthesis of cyclobutylboronates is still a great challenge.[90] In this section we will cover the stereoselective methodologies to synthetize cyclobutylboronates. This topic is divided into two sections. The first one describes synthetic methods that are just diastereoselective, that is, those that do not allow for the preparation of enantiomerically enriched compounds. The second section compiles the existing asymmetric methodologies for the preparation of cyclobutylboronates, that is, those that allow for the preparation of enantiomerically enriched compounds.

2.1.6.1. Diastereoselective Synthesis of Cyclobutylboronates.

Comparing the number of different methodologies to prepare cyclopropylboronates, cyclobutyl derivatives have received considerably less attention. In 2010, Ito and coworkers, in a very elegant work, developed the stereospecific synthesis of cyclobutylboronates through a copper-

[90] Martin-Heras, V.; Parra, A.; Tortosa, M. *Synthesis*, **2018**, *50*, 470-484.

catalyzed borylation of homoallylic sulfonates (**Scheme *2-26***).[91] The initial insertion of the double bond into the copper-boron complex allows for the formation an alkylcopper intermediate that cyclized to form a cyclobutylboronate. Both *syn* and *anti*-derivatives could be obtained by switching the double bond geometry. The limitation of this method is that either a phenyl or a silyl group in the alkene is necessary for the reaction to occur.

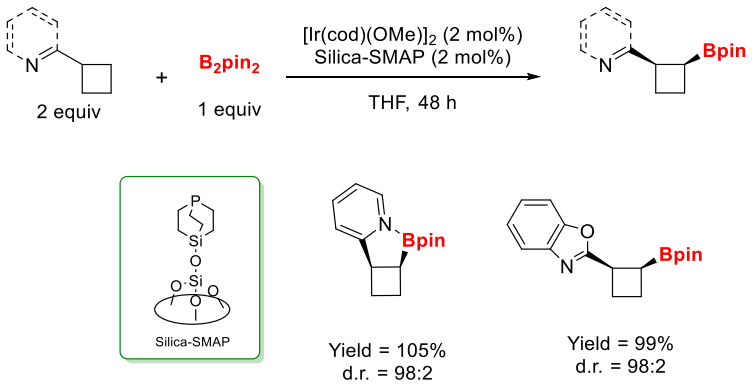


Scheme 2-26: Copper catalyzed stereospecific synthesis of cyclobutylboronates.

Sawamura and coworkers reported a diastereoselective method for the C-H borylation of cyclobutanes (**Scheme *2-27***).[92] Nitrogen-containing substituents in the cyclobutane ring, such as pyridyl or benzoxazolyl, are required as directing groups to obtain high diastereoselectivities. As catalyst they used a silica-supported monophosphane-Ir complex and

[91] Ito, H.; Toyoda, T.; Sawamura, M. *J. Am. Chem. Soc.* **2010**, *132*, 5990-5992.
[92] Murakami, R.; Tsunoda, K.; Iwai, T.; Sawamura, M. *Chem. Eur. J.* **2014**, *20*, 13127-13131.

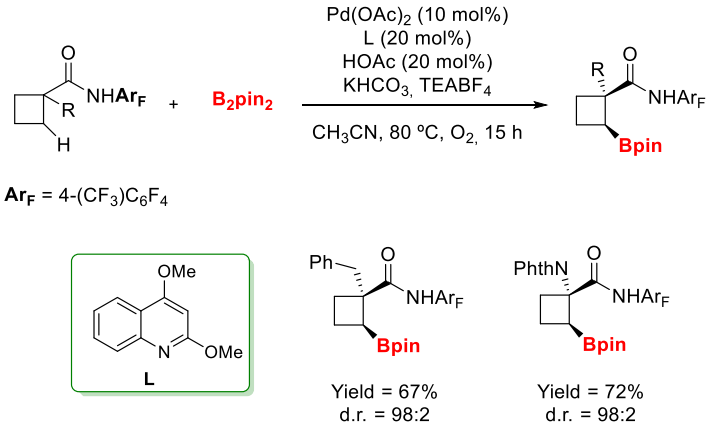
B_2pin_2 as boron source. The pinacolborane produced after the borylation also worked as borylating agent, therefore yields could be up to 200%.



Scheme 2-27: Stereoselective C-H borylation of cyclobutanes catalyzed by silica supported Ir catalyst.

It was in 2016, when Yu and coworkers reported the Pd-catalyzed *β*-borylation of amides (**Scheme *2-28***).[93] The reaction is promoted by quinoline-based ligands and among the wide range of compounds compatible with this methodology, cyclobutylamides afforded excellent results. Cyclobutylboronates were synthetized with excellent yields as single diastereomers.

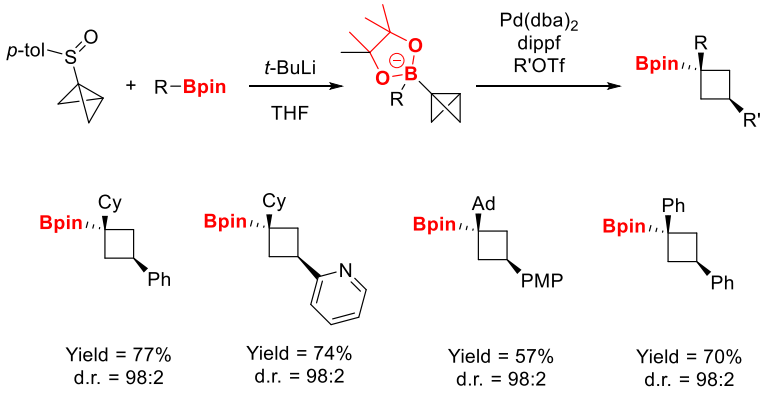
[93] He, J.; Jiang, H.; Takise, R.; Zhu, R. Y.; Chen, G.; Dai, H. X.; Dhar, T. G. M.; Shi, J.; Zhang, H.; Cheng, P. T. W.; Yu, J. Q. *Angew. Chem. Int. Ed.* **2016**, *55*, 785-789.



Scheme 2-28: Pd-catalyzed C-H borylation of cyclobutanes.

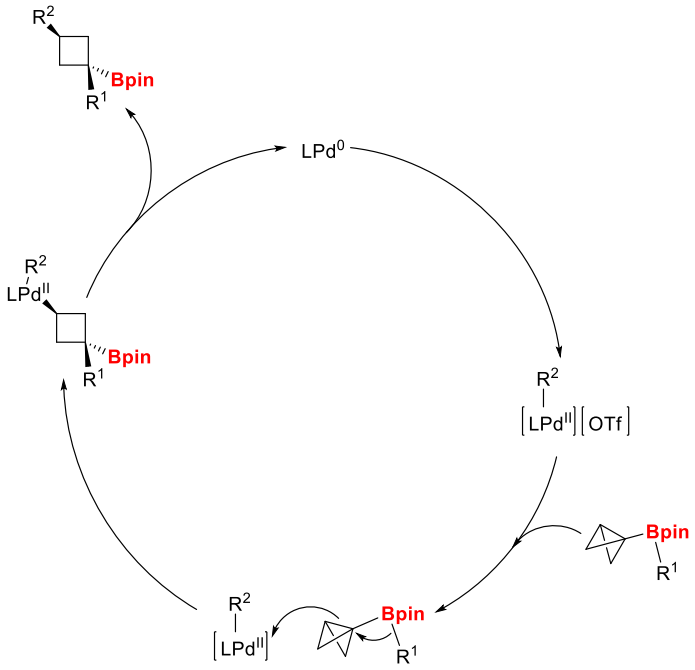
Recently, Aggarwald and coworkers published a palladium catalyzed cross-coupling where they succeeded into the carbopalladation of a strained σ-bond of bicyclo[1.1.0]butyl boronate complexes, introducing at the same time an aryl unit and a boronic ester across the mentioned σ-bond. With this methodology they synthetized arylcyclobutylboronates with excellent diastereocontrol (**Scheme *2-29***).[94]

[94] Fawcett, A.; Biberger, T.; Aggarwal, V. K. *Nat. Chem.* **2019**, *11*, 117-122.



Scheme 2-29: Carbopalladation of σ-bonds to synthesize substituted cyclobutylboronates.

The mechanism they proposed started by the oxidative addition of the aryl triflate to the palladium(0) complex. Then, the palladium(II) complex attacked from the exo face of the bicyclo[1.1.0]butyl moiety inducing a 1,2-metallate rearrangement, where there is a simultaneous cleavage of the C-C bond, 1,2-migration of the substituent in the boronate complex to the α-carbon and formation of the C-Pd bond at the β-carbon. The last step is the reductive elimination to give the desired cyclobutylboronate and start again the catalytic cycle (**Scheme *2-30***).

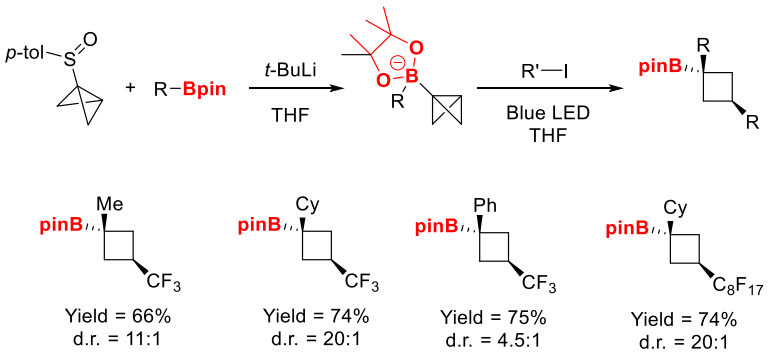


Scheme 2-30: Mechanism for the carbopalladation of C-C σ-bonds in strained boronate complexes.

Recently, Aggarwal and Silvi, reported the radical addition of different alkyl iodines to strained σ-bonds of bicyclo[1.1.0]butyl boronate complexes. They succeeded in the diastereoselective synthesis of cyclobutylboronates with moderate to excellent results without the use of any metal catalyst (**Scheme *2-31***).[95] The mechanism is similar to that explained in **Scheme *2-30***. They proposed that the radical formed from the alkyl iodine under visible light irradiation added to the central bond of the bicyclo[1.1.0]butyl unit leading to a radical anion. This radical anion underwent a SET process with another molecule of alkyl iodine forming a

[95] Silvi, M.; Aggarwal, V. K. *J. Am. Chem. Soc.* **2019**, *141*, 9511-9515.

zwitterionic specie, which underwent a 1,2-metalate rearrangement to form the desired cyclobutylboronate.

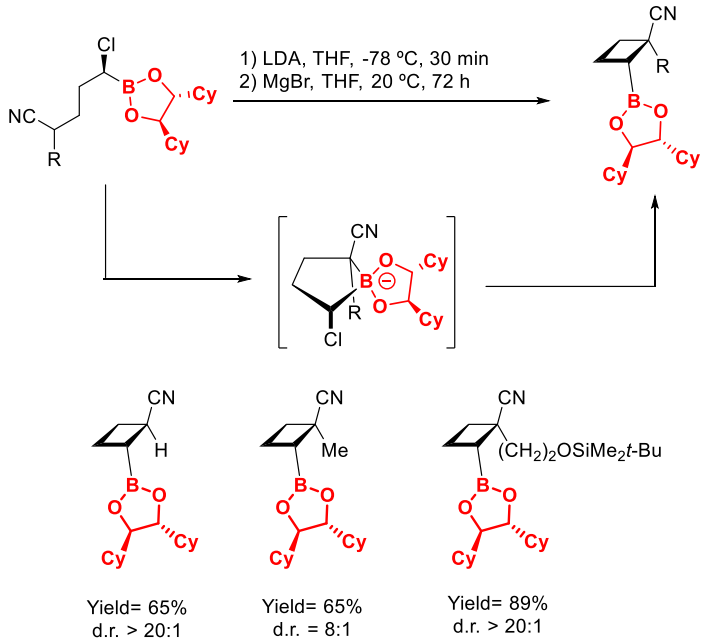


Scheme 2-31: Radical addition to strained σ-bonds to synthesis cyclobutylboronates.

2.1.6.2. Asymmetric Synthesis of Cyclobutylboronates.

Similarly, the asymmetric synthesis of cyclobutylboronates has been much less studied than the asymmetric synthesis of cyclopropylboronates. The first example was reported in 1999, when Matteson and coworkers published the first synthesis of enantiomerically enriched boron-containing cyclobutanes (**Scheme *2-32***).[96] Deprotonation of an enantiopure δ-cyano α-chloroboronate with LDA provided a cyclic boronate that evolved to the desired cyclobutylboronate upon treatment with $MgBr_2$.

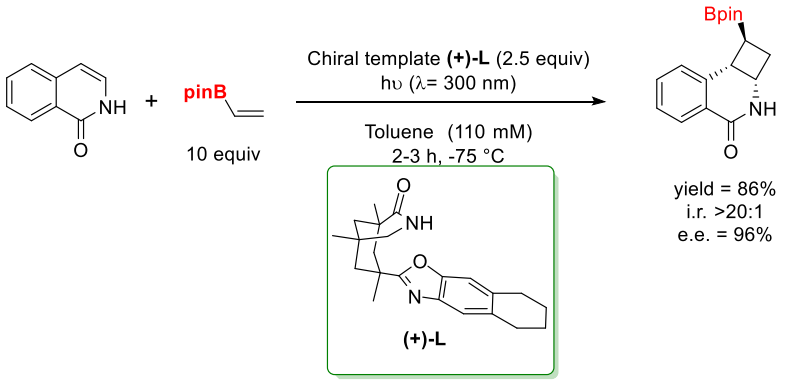
[96] Man, H. W.; Hiscox, W. C.; Matteson, D. S. *Org. Lett.* **1999**, *1*, 379-381.



Scheme 2-32: Stereoselective synthesis of cyclobutylboronates.

Making good use of the opportunities offered by photochemistry, Bach and coworkers developed an enantioselective [2+2] cycloaddition. They used an innovative chiral template for the reaction, and under 300 nm wavelength light the desired cyclobutylboronate is formed with excellent results and almost perfect stereocontrol (**Scheme *2-33***).[97] The drawbacks of this reaction is that 2.5 equivalents of chiral template are needed, as well as 10 equivalents of vinylboronate.

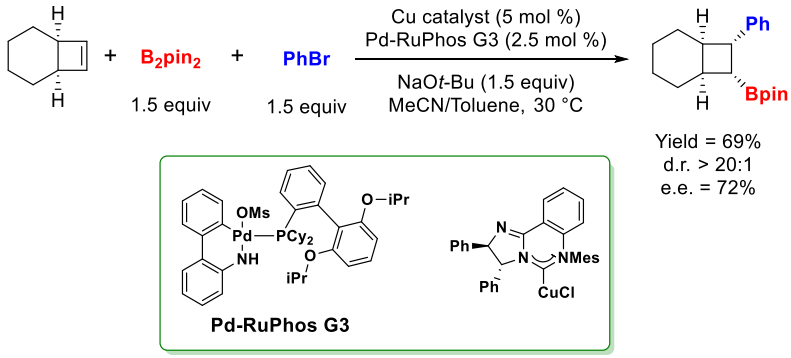
[97] Coote, S. C.; Bach, T. *J. Am. Chem. Soc.* **2013**, *135*, 14948-14951.



Scheme 2-33: Enantioselective [2+2] photochemical synthesis of cyclobutylboronate.

Recently, after the results presented in this chapter were reported, Logan and Brown used Pd-Ruphos G3 and a copper(I) complex in combination to create a catalytic system capable of perform the enantioselective arylboration of alkenes. Concerning this thesis, they reported the formation of a bicyclic cyclobutylboronate with good yield and moderate enantioselectivity (**Scheme *2-34***).[98]

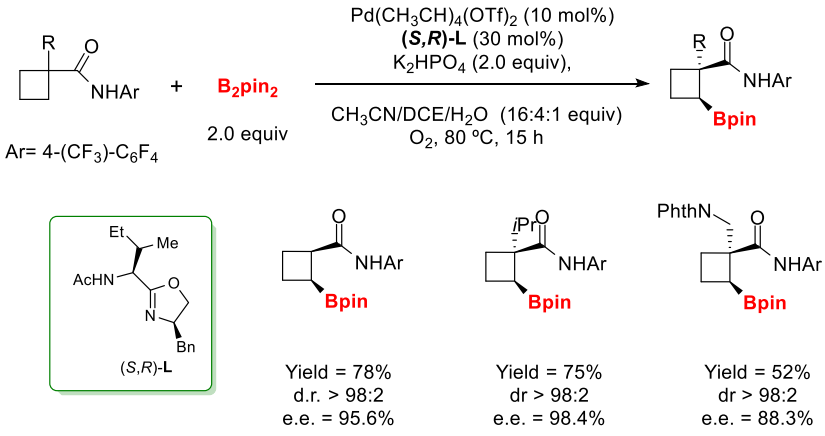
[98] Logan, K. M.; Brown, M. K. *Angew. Chem. Int. Ed.* **2017**, *56*, 851-855.



Scheme 2-34: Pd/Cu catalyzed enantioselective arylborylation of alkenes.

In the same year, Yu and coworkers reported the enantioselective Pd-catalyzed C-H activation of cyclobutylamides. As in their previous report (**Scheme *2-28***),[93] the amide moiety worked as directing group. In the present case, they used a chiral bidentate ligand to obtain the desired cyclobutylboronates with excellent yields and enantioselectivities (**Scheme *2-35***).[99]

[99] He, J.; Shao, Q.; Wu, Q.; Yu, J. Q. *J. Am. Chem. Soc.* **2017**, *139*, 3344-3347.



Scheme 2-35: Enantioselective C-H borylation of cyclobutylamides.

2.2. Enantioselective Synthesis of Cyclobutylboronates via a Copper-Catalyzed Desymmetrization Approach.

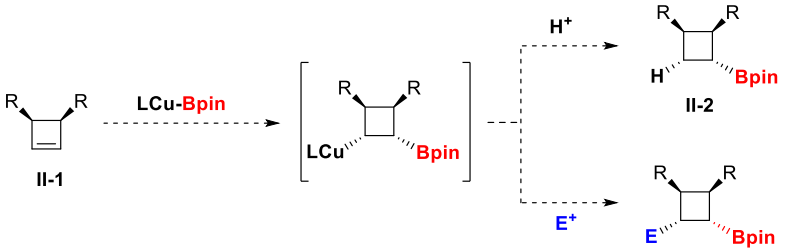
2.2.1. Objectives.

At the beginning of this Doctoral Thesis there were only two reports for the synthesis of enantiomerically enriched cyclobutylboronates (**Scheme *2-32*** and **Scheme *2-33***)[96,97], none of them using a catalytic amount of a chiral source. Eager to broad the toolbox to prepare these useful, nevertheless difficult-to-prepare compounds, we decided to explore an entirely new approach. We thought to apply our experience in copper-catalyzed borylations[66,69,100] and envisioned the possibility of access cyclobutylboronates through a desymmetrization of *meso*-cyclobutenes. If successful, our method would be the first catalytic enantioselective approach for the synthesis of cyclobutylboronates. Beside the importance of the products, we were also intrigued about the behavior of cyclobutenes under copper-catalyzed borylation conditions. Our idea was supported by the successful copper-catalyzed borylation of cyclopropenes previously resported in our group.[66] However, reactivity, diastereoselectivity and enantioselectivity were not obvious parameters to control when moving from a three to a four-membered alkene. Indeed, the evidence that shows that *meso*-cyclobutenes are challenging substrates is that they had been scarcely used in metal-catalyzed transformations, and virtually unexplored in asymmetric catalysis. With these ideas in mind, we proposed the following objectives for this chapter (**Scheme *2-36***):

- To develop a diastero- and enantioselective copper-catalyzed borylation of *meso*-cyclobutenes to produce cyclobutylboronates with three stereogenic centers.

[100] a) Lopez, A.; Parra, A.; Jarava-Barrera, C.; Tortosa, M. *Chem. Comm.* **2015**, *51*, 17684-17687. b) Jarava-Barrera, C.; Parra, A.; Lopez, A; Cruz-Acosta, F.; Collado-Sanz, D.; Cárdenas, D. J.; Tortosa, M. *ACS Catal.* **2016**, *6*, 442-446.

- To explore the possibility of trapping the cyclobutylcopper intermediate with electrophiles different than proton. If this approach is successful, we could access cyclobutylboronates with up to four contiguous stereogenic centers.



Scheme 2-36: Objectives of this chapter.

2.2.2. Synthesis of Starting Materials.

First, we prepared a series of *meso*-cyclobutenes **II-1a-l** (**Figure *2-7***) to study the copper-catalyzed borylation. To do so, we followed different reported procedures depending on the substituents attached to the ring.

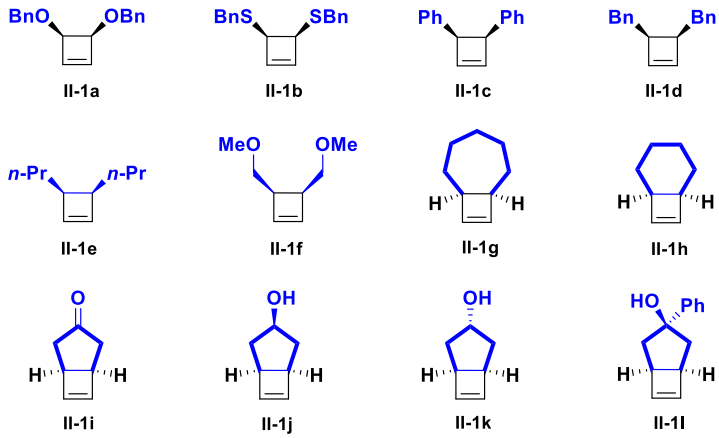
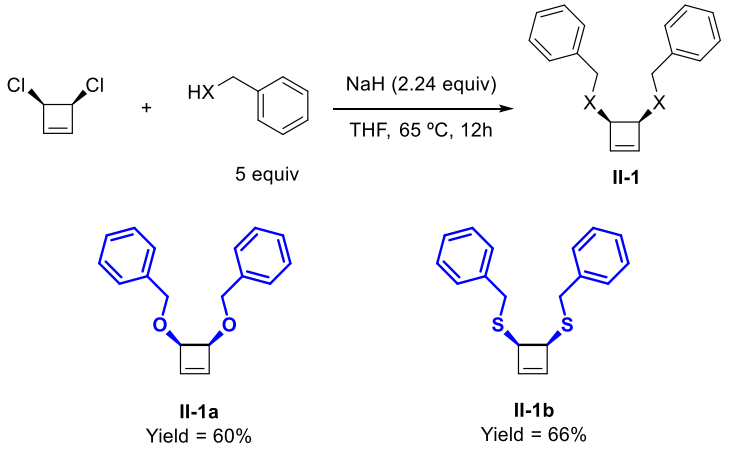


Figure 2-7: Prepared meso-cyclobutenes.

Cyclobutene **II-1a**, with two benzyloxy substituents, was synthetized from commercially available *cis*-dichlorocyclobutene in only one step, making this synthesis very convenient (**Scheme *2-37***).[101] We used the same procedure to synthetize cyclobutene **II-1b**, with to benzylthionyl substituents in the structure.

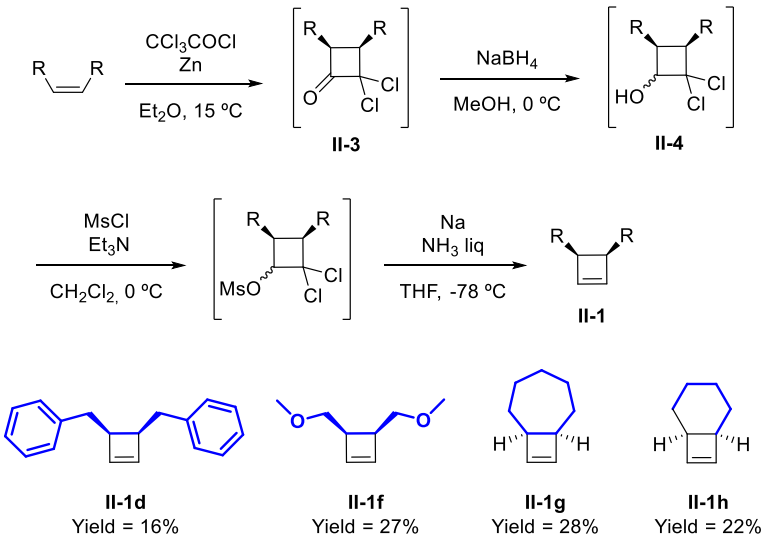
[101] A. H.; Lombardi, P. J.; O'Brien, R. V.; Zhugralin, A. R. *J. Am. Chem. Soc.* **2009**, *131*, 8378-8379.



Scheme 2-37: Synthesis of cyclobutenes **II-1a** and **II-1b.**

Cyclobutenes **II-1d**, **II-1f**, **II-1g** and **II-1h** were prepared following a modified reported procedure.[102] The sequence started with the *in situ* formation of dichloroketene from trichloroacetyl chloride and zinc. [2+2] cycloaddition between the corresponding *Z*-alkene and dichloroketene formed compounds **II-3**. The ketone was reduced with $NaBH_4$, forming alcohols **II-4**. By a sequence of mesylation and elimination with Na/NH_3, cyclobutenes **II-1** were finally formed (**Scheme *2-38***). Only one purification step was needed, and the yields indicated are global yields.

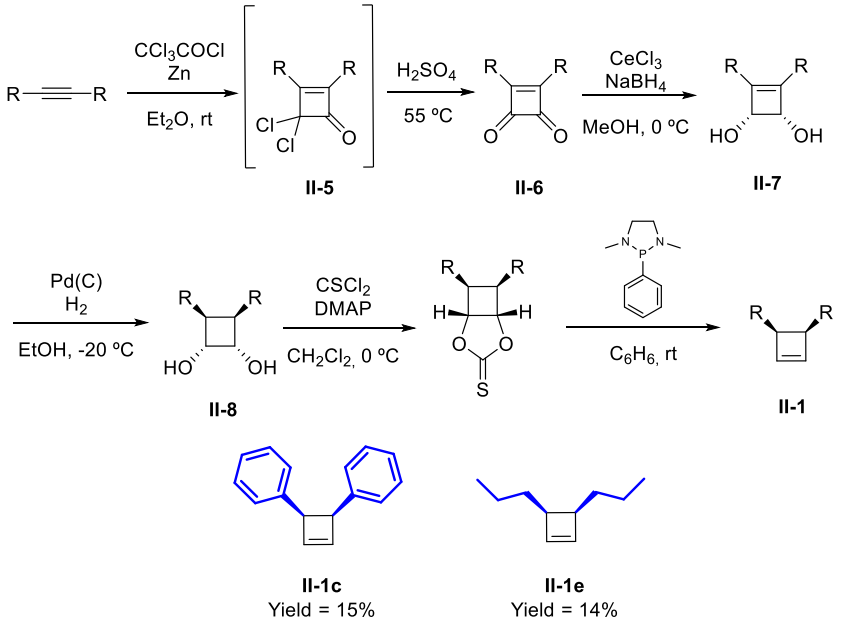
[102] Baldwin, J. E.; Gallagher, S. S.; Leber, P. A.; Raghavan, A. S.; Shukla, R. *J. Org. Chem.* **2004**, *69*, 7212-7219.



Scheme 2-38: Synthesis of Cyclobutenes **II-1d**, **II-1f**, **II-1g** and **II-1h.**

Compounds **II-1c** and **II-1e** (**Scheme *2-39***), were prepared following a reported procedure.[103] The sequence started as before with the *in situ* formation of the dichloroketene from trichloroacetyl chloride and zinc. Alkynes reacted with the *in situ* formed dichloroketene, forming the corresponding dichlorocyclobutenones **II-5**, which were oxidized to diketones **II-6** with H_2SO_4. Then, by Luche reduction with $NaBH_4/CeCl_3$ the *cis* diols **II-7** were formed diastereoselective, and the double bond was reduced by Pd/H_2 to form cyclobutanediols **II-8**. To form the desired cyclobutenes **II-1**, a Corey-Hopkins elimination was performed.[104]

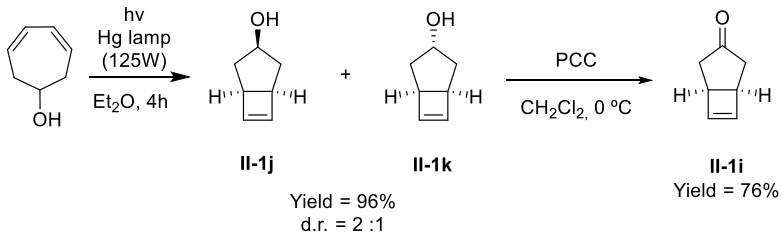
[103] Hasegawa, M.; Murakami, M. *J. Org. Chem*. **2007**, *72*, 3764.
[104] Corey, E. J.; Hopkins, P. B. *Tetrahedron Lett.* **1982**, *23*, 1979-1982.



Scheme 2-39: Synthesis of cyclobutenes **II-1c** and **II-1e**.

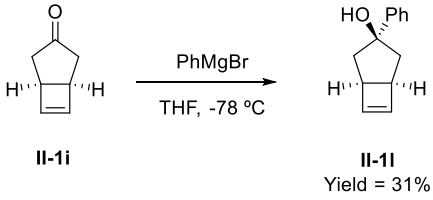
Cyclobutenes **II-1j**, **II-1k** and **II-1i** were synthetized following a reported procedure (**Scheme *2-40***).[105] From 5-heptadienol, obtained from reduction of tropone, cyclobutenes **II-1j** and **II-1k** were prepared, as a separable mixture of diastereoisomers, through a intramolecular photochemical disrotatory cyclization. This mixture could be oxidized to obtain cyclobutene **II-1i**.

[105] Zhang, Z.; Song, Q. P.; Wang, G. W.; Luh, T.Y. *ARKIVOC*, **2009**, *7*, 229-236.



Scheme 2-40: Synthesis of cyclobutene **II-1i**, **II-1j** and **II-1k**.

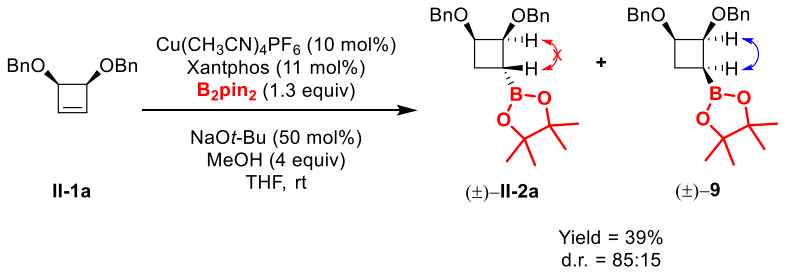
Finally, cyclobutene **II-1l** was prepared through diastereoselective attack of phenylmagnesium bromide to **II-1i** (**Scheme *2-41***).



Scheme 2-41: Synthesis of cyclobutene **II-1l.**

2.2.3. Copper-Catalyzed Borylation of Cyclobutenes: Preliminary Results.

We chose cyclobutene **II-1a** as the model substrate for the enantioselective synthesis of cyclobutylboroantes. Before studying the enantioselective approach, we first explored the reactivity of cyclobutene **II-1a** under copper-catalyzed conditions using a non-chiral ligand. Treatment of cyclobutene **II-1a** with 1.3 equivalents of B_2pin_2 in the presence of $Cu(CH_3CN)_4PF_6$ (10 mol%) as copper source, xantphos (11 mol%) as ligand, NaO*t*-Bu (50 mol%) as base in THF, led to a diastereomeric mixture of cyclobutylboronates (d.r. = 85:15) in low yield (**Scheme *2-42***). Although the result was not as good as expected, this experiment allowed us to obtain samples of both diastereoisomers, determined the relative configuration through NOE analysis and encouraged us to search for conditions to develop the enantioselective version.



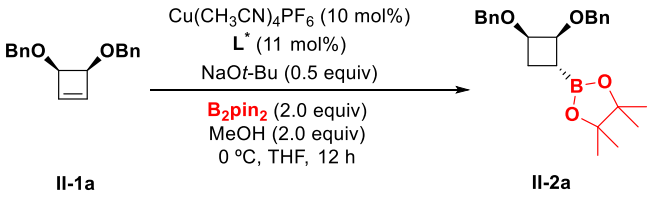
Scheme 2-42: Diastereoselective copper-catalyzed borylation of cyclobutene **II-1a**.

2.2.4. Copper-Catalyzed Borylation of Cyclobutenes: Screening of Conditions.

To test the feasibility of the enantioselective version of the reaction, we selected a set of chiral commercially available phosphines with different steric and electronic properties (**Table *2-1***).

In the first attempt, we were delighted to see that the reaction of cyclobutene **II-1a** and 2 equivalents of bis(pinacolato)diboron under 10 mol% of $Cu(CH_3CN)_4PF_6$ as copper source, (*R*)-BINAP (11 mol%) as ligand and *t*-BuONa (50 mol%) as base in THF, lead to cyclobutylboronate **II-2a** with high yield and excellent diastereomeric (93:7) and enantiomeric ratio (96:4) (**Table *2-1***, entry 1). We soon realized that although results with BINAP were good, Segphos derivatives provided superior results (**Table *2-1***, entries 2-4). With ferrocene derivative **L5** and quinoline ligand QuinoxP*, we observed a significant drop in the enantioselectivity and lower diastereoselectivity. With these results in hand, we chose (*R*)-DM-Segphos as the ligand of choice, which provide cyclobutylboronate **II-2a** with 96% isolated yield and excellent stereocontrol (**Table *2-1***, entry 3, d.r. > 98:2, e.r. = 99:1).

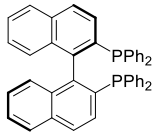
Table 2-1: Ligand Optimization.



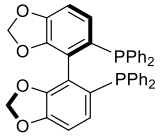
II-1a **II-2a**

Entry	L*	d.r.[b]	e.r.[c]	Yield (%)[d]
1	L1	93:7	96:4	76
2	L2	>98:2	94:6	93
3	L3	>98:2	99:1	96
4	L4	>98:2	96:4	90
5	L5	95:5	15:85	84
6	L6	90:10	82:18	81

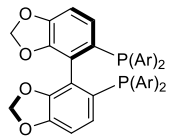
[a] Reaction conditions: **II-1a** (0.1 mmol), B_2pin_2 (0.20 mmol), NaO*t*-Bu (50 mol%), $Cu(CH_3CN)_4PF_6$ (10 mol%), **L*** (11 mol%), MeOH (0.2 mmol), THF (0.2 M). [b]d.r. determined by ^{1}H-NMR analysis. [c]e.r. determined by chiral SFC. [d] Yield of isolated **II-2a**.

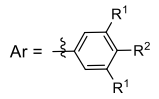


(*R*)-BINAP
L1

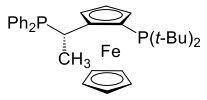


(*R*)-SEGPHOS
L2

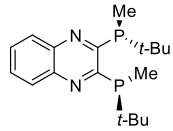




(*R*)-DM-SEGPHOS **L3**: R^1 = Me; R^2 = H
(*R*)-DTBM-SEGPHOS **L4**: R^1 = *t*-Bu; R^2 = OMe



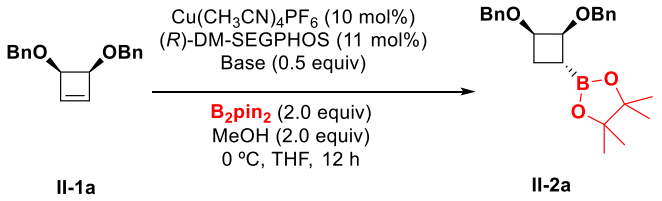
L5



(*R,R*)-QuinoxP
L6

Attempts to change the base did not provide better results (**Table *2-2***). KO*t*-Bu gave the desired product with good yield (81%) and excellent enantioselectivity (99:1), but with a diastereoselectivity of 80:20 (**Table *2-2***, entry 2). NaOMe afforded the product with an excellent enantioselectivity of 98:1, but the yield and diastereoselectivity were significantly lower (**Table *2-2***, entry 3).

Table 2-2: Base Optimization.



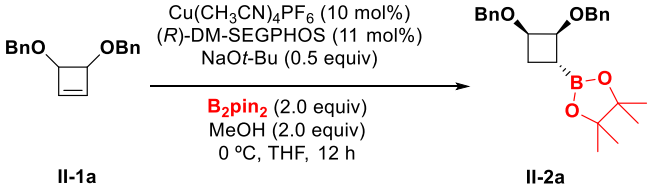
II-1a **II-2a**

Entry	Base	d.r.[b]	e.r.[c]	Yield (%)[d]
1	NaO*t*-Bu	>98:2	99:1	96
2	KO*t*-Bu	80:20	99:1	81
3	NaOMe	80:20	98:2	44

[a] Reaction conditions: **II-1a** (0.1 mmol), B_2pin_2 (0.20 mmol), Base (50 mol%), $Cu(CH_3CN)_4PF_6$ (10 mol%), (*R*)-DM-SEGPHOS (11 mol%), MeOH (0.2 mmol), THF (0.2 M). [b]d.r. determined by ^{1}H-NMR analysis. [c]e.r. determined by chiral SFC. [d] Yield of isolated **II-2a**.

Copper(I) chloride provided similar results, however the diastereomeric ratio and the yield were slightly lower than when using $Cu(CH_3CN)PF_6$ (**Table *2-3***, entry 2). Carrying out the reaction with 5 mol% of Cu(I), provided inferior results (**Table *2-3***, entry 3). Finally, reducing the equivalents of B_2pin_2 to 1.1, provided the product with excellent stereocontrol but only 60% yield (**Table *2-3***, entry 4).

Table 2-3: Reaction Optimization.



II-1a II-2a

Entry	Change in other parameters	d.r.[b]	e.r.[c]	Yield (%)[d]
1	-	>98:2	99:1	96
2	CuCl (10 mol%)	94:6	98:2	90
3	$Cu(CH_3CN)PF_6$ (5 mol%)	90:10	95:5	70
4	1.1 equiv B_2pin_2	>98:2	99:1	60

[a] Reaction conditions: **II-1a** (0.1 mmol), B_2pin_2 (0.20 mmol), NaO*t*-Bu (50 mol%), $Cu(CH_3CN)_4PF_6$ (10 mol%), (*R*)-DM-SEGPHOS (11 mol%), MeOH (0.2 mmol), THF (0.2 M). [b]d.r. determined by ^{1}H-NMR analysis. [c]e.r. determined by chiral SFC. [d] Yield of isolated **II-2a**.

2.2.5. Scope of the Reaction.

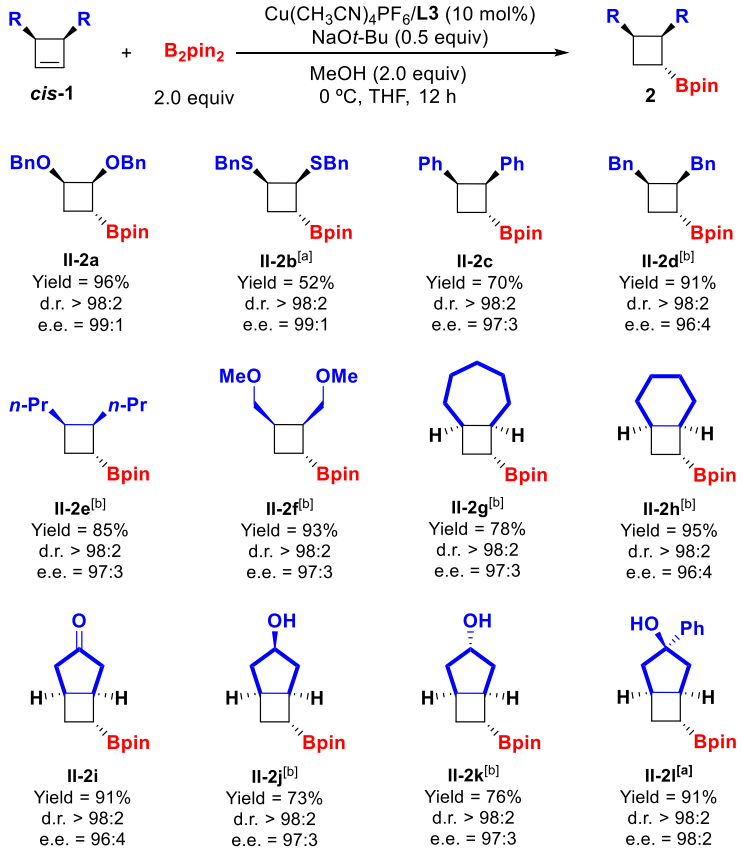
To study the scope of the reaction, a variety of disubstituted *meso*-cyclobutenes (**II-1**) were tested with the optimized copper-catalyzed borylation conditions (**Scheme *2-43***).

When we applied the optimal conditions to cyclobutane **II-1b**, we observed a significant decrease in the yield (22%) but the stereocontrol was still excellent. We reasoned that sulfur atoms could coordinate to the copper catalyst, poisoning it and stopping the catalytic cycle. We reasoned that a ligand bulkier than DM-Segphos, could provide better results, minimizing the coordination of the sulfur atoms. Gratifyingly, when we used (*R*)-DTBM-Segphos (**L4**) as ligand, cyclobutylboronate **II-2b** was obtained with excellent stereocontrol and better yield (52%). Aromatic substituents were compatible with the reaction conditions and compound **II-2c**, was prepared with excellent results. Cyclobutenes **II-1d** and **II-1e**, with alkyl groups as substituents, yielded the borylation products with excellent stereocontrol and yield, independently of the steric hindrance of the alkyl chain. Moreover, alkyl chains with coordinating alkoxy groups, produced the corresponding cyclobutylboronate **II-2f** with any erosion of the yield or the stereoselectivity.

Bicyclic compounds were compatible with the reaction conditions and a variety of bicyclic cyclobutenes were tested. Cyclohexyl and cycloheptyl rings fused with the cyclobutene (compounds **II-1g** and **II-1h**) were suitable substrates for the borylation. We were pleased to see that the presence of unprotected ketones did not affect the reaction, yielding the borylated product **II-2i** with 91% yield and excellent stereocontrol, without traces of the borylated ketone.[106] Cyclobutylboronates **II-2j** and **II-2k**, were prepared from the correspondent cyclobutenes, with excellent results. The

[106] McIntosh, M. L.; Moore, C. M.; Clark, T. B. *Org. Lett.* **2010**, *12*, 1996-1999.

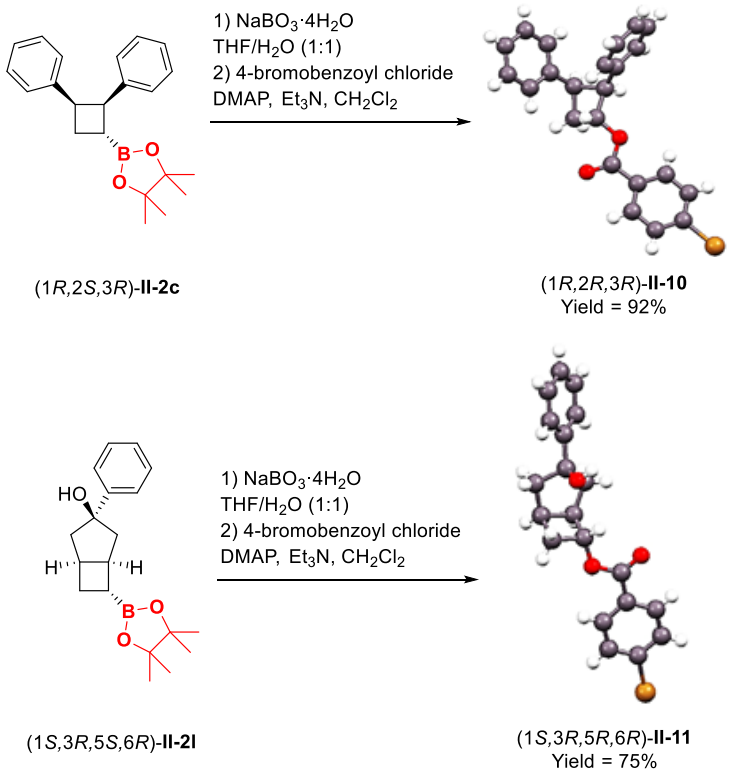
presence of a free alcohol in the bicyclic structure, did not affect the outcome of the reaction. Compound **II-2l**, with a quaternary center, yielded the borylated product with almost perfect stereocontrol and excellent yield. In the last three examples, the creation of four stereogenic centers in the molecule was achieved in only one step of synthesis, with complete stereoselectivity.



[a] L4 was used instead of L3. [b] The reaction was carried out at -20 °C.

Scheme 2-43: Scope of the enantioselective copper-catalyzed borylation of *meso*-cyclobutenes.

The absolute configuration of (*R*,*S*,*R*)-**II-2c** and (*S*,*R*,*S*,*R*)-**II-2l** were determined from single crystal X-ray crystallography of *p*-bromobenzoates (*R*,*R*,*R*)-**II-10**[107] and (*S*,*R*,*R*,*R*)-**II-11**[108] derivatives (**Scheme *2-44***). Oxidation of the carbon-boron bond with sodium perborate, followed by benzoylation with 4-bromobenzoyl chloride afforded compounds (*R*,*R*,*R*)-**II-10** and (*S*,*R*,*R*,*R*)-**II-11**. The absolute configuration of all the other cyclobutylboronates was assigned by analogy.



Scheme 2-44: Determination of the absolute configuration by X-ray crystallography.

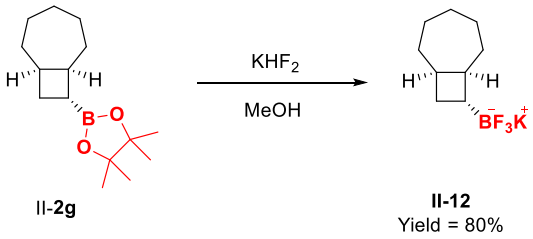
[107] CCDC 1442992 contains the supplementary crystallographic data. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html

[108] CCDC 1441995 contains the supplementary crystallographic data. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html

2.2.6. Derivatizations.

Tu further demonstrate the utility of the synthetized cyclobutylboronates we designed a series of transformations, in order to converted them in useful intermediates.

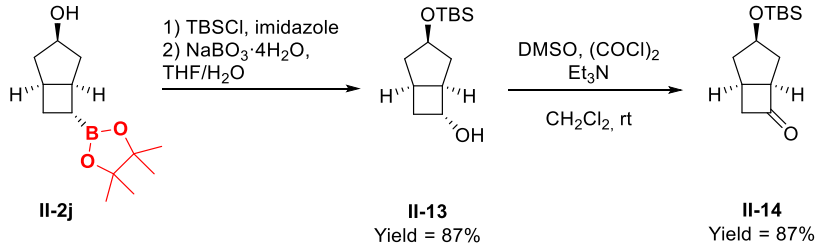
First, we successfully transformed cyclobutylboronate **II-2g** into the correspondent trifluoroborate salt **II-12**. These salts have been successfully employed in a variety of cross-coupling reactions, as more stable equivalents of boronic acids (**Scheme *2-45***).[109]



Scheme 2-45: Formation of trifluoroborate salt **II-12**.

Secondly, we have transformed cyclobutylboronate **II-2j**, into enantiomerically enriched cyclobutanone **II-14** by protection of the alcohol with *tert*-butyldimethylsilyl chloride and double oxidation of the C-B bond to the ketone **II-14** (**Scheme *2-46***). We have used ketone **II-14** as intermediate for the preparation of some valuable compounds.

[109] a) Fang, G. -H.; Yan Z. -J.; Deng, M. -Z. *Org. Lett.* **2004**, *6*, 357-360. b) Molander, G. A.; Ellis, N. *Acc. Chem. Res.* **2007**, *40*, 275-286. c) Darses, S.; Genet, J. P. *Chem. Rev*. **2008**, *108*, 288-325. d) Molander, G. A., Gormisky, P. E. *J. Org. Chem.* **2008**, *73*, 7481-7485.



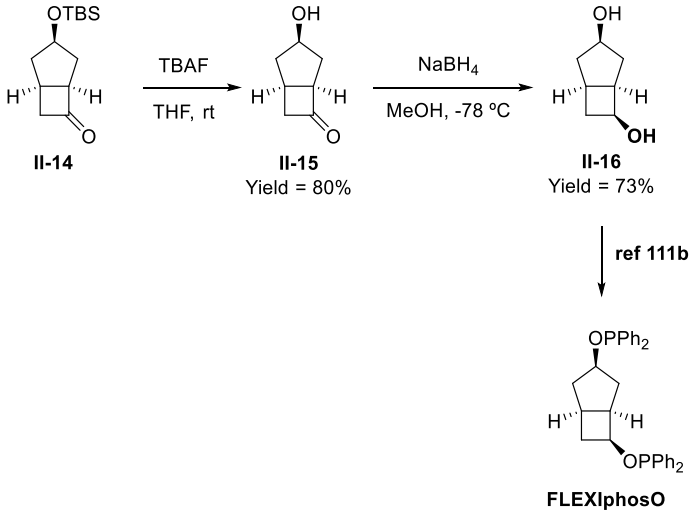
Scheme 2-46: Synthesis of cyclobutanone **II-14.**

We have transformed cyclobutanone **II-14** into diol **II-16**, in only two steps (**Scheme *2-47***), being this synthesis the very first catalytic enantioselective synthesis of this compound. Previous synthesis of this compounds depended on kinetic resolution of the racemic compound. This diol is a precursor of the chiral ligand FLEXIphosO,[110] useful in rhodium-catalyzed asymmetric hydrogenations[111] and 1,6-diene cycloisomerization catalyzed by palladium.[112]

[110] Fairlamb, I. J. S.; Tommasi, S.; Moulton, B. E.; Zheng, W.; Lin, Z.; Whitwood, A. C. *Eur. J. Inorg. Chem.* **2007**, 3173-3178.

[111] a) Adger, B.; Berens, U.; Griffiths, M. J.; Kelly, M. J.; McCague, R.; Miller, J. A.; Palmer, C. F.; Roberts, S. M.; Selke, R.; Vitinius, U.; Ward, G. *Chem. Commun.* **1997**, 1713-1714. b) Derrien, N.; Dousson, C. B.; Roberts, S. M.; Berens, U.; Burk, M. J.; Ohff, M. *Tetrahedron: Asymmetry* **1999**, *10*, 3341-3352.

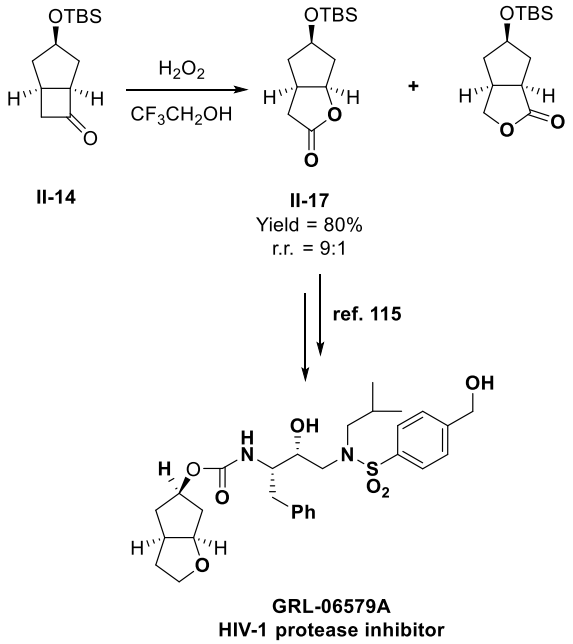
[112] a) Fairlamb, I. J. S.; Grant, S.; Whitwood, A. C.; Whitthall, J.; Batsanov, A. S.; Collings, J. C. *J. Organomet. Chem.* **2005**, *690*, 4462-4477. b) Fairlamb, I. J. S.; Grant, S.; Tommasi, S.; Lynam, J. M.; Bandini, M.; Dong, H.; Lin, Z.; Whitwood, A. *Adv. Synth. Catal.* **2006**, *348*, 2515-2530.



Scheme 2-47: Synthesis of diol **II-16**.

We also have performed the regioselective Baeyer-Villiger oxidation of cyclobutanone **II-14** to obtain Corey lactone **II-17** (**Scheme *2-48***).[113] In a first attempt, we tried to perform the Baeyer-Villiger oxidation using *m*CPBA, but we observed that although the conversion was complete the regioselectivity was not good enough (r.r. = 2.8:1). We also tried using $SbCl_5$ along with ethyl diazoacetate, but a complicated mixture was formed. Finally, using H_2O_2 in trifluoroethanol, we achieved the desired transformation with excellent regioselectivity (r.r. = 9:1).[114] Lactone **II-17** is an intermediate in the synthesis of the HIV-1 protease inhibitor GRL-06579A.[115]

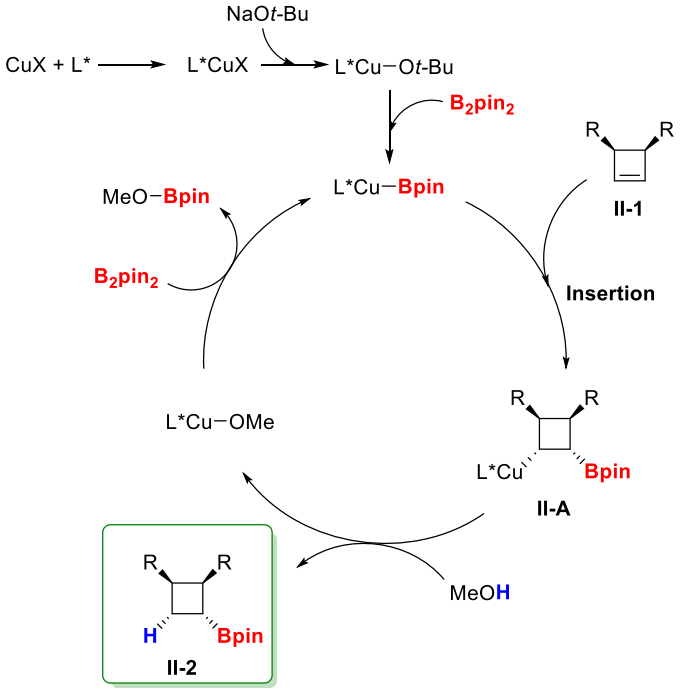
[113] Corey, E. J.; Weinshenker, N. M.; Schaaf, T. K.; Huber, W. *J. Am. Chem. Soc.* **1969**, *91*, 5675-5677.
[114] Depre, D.; Chen, L. Y.; Ghosez, L. *Tetrahedron*, **2003**, *59*, 6797-6812.
[115] Ghosh, A. K.; Takayama, J. *Tetrahedron Lett.* **2008**, *49*, 3409-3412.



Scheme 2-48: Synthesis of Corey lactone **II-17**.

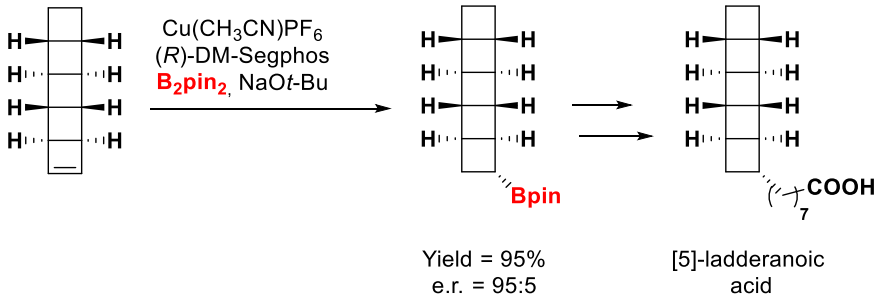
2.2.7. Mechanistic Proposal.

A plausible mechanism for the copper(I)-catalyzed borylation of cyclobutenes is proposed in **Scheme 2-49**. First, the reaction between copper(I) salt, the ligand and sodium *tert*-butoxide formed a copper alkoxide. This alkoxide (L*Cu-O*t*-Bu) could undergo a σ-bond metathesis reaction with bis(pinacolato)diboron to form a chiral copper-boryl complex (L*Cu-Bpin). Then, insertion of the cyclobutene into the copper-boryl complex would afford cyclobutyl copper intermediate **II-A**. Reaction with MeOH would provide the hydroboration product and copper-methoxide (L*Cu-OMe) that would regenerate the catalytic cycle.



Scheme 2-49: Mechanism for the copper-catalyzed borylation of cyclobutenes.

This methodology has been used by Burns and co-workers as key step in the synthesis of [5]-ladderanoic acid (**Scheme *2-50***).[116]



Scheme 2-50: Synthesis of [5]-ladderanoic acid.

[116] Mercer, J. A. M; Cohen, C. M.; Shuken, S. R.; Wagner, A. M.; Smith, M. W.; Moss III, F. R.; Smith, M. D.; Vahala, R.; Gonzalez-Martinez, A.; Boxer, S. G.; Burns, N. Z. *J. Am. Chem. Soc.* **2016**, *138*, 15845-15848.

2.3. Enantioselective Carboboration of Cyclobutenes.

2.3.1. Introduction and Objectives.

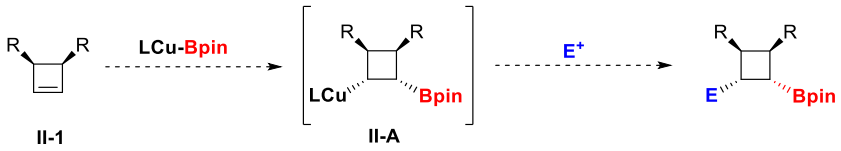
Looking back at the proposed mechanism (**Scheme *2-49***), we thought about the possibility of trapping the cyclobutylcopper intermediate **II-A** with an electrophile different than proton (**Scheme *2-51***). If we succeeded in this endeavor, we would have developed a borylation of the double bond in combination with another bond-forming process.[117] Previously, in our group, the copper-catalyzed carboboration of alkynes was successfully performed.[118] Other groups have also performed the copper-catalyzed carboboration of diverse motifs.[119] But this transformation, as well as with the hydroboration, has never been performed in cyclobutenes. The expected products would be cyclobutylboronates with four contiguous stereocenters. The creation of four new stereocenters in a single step would be an important contribution to the field. The objective of this chapter is to perform an enantioselective copper-catalyzed carboboration of *meso*-

[117] For reviews see: a) Cuenca, A. B.; Shishido, R.; Ito, H.; Fernandez, E. *Chem. Soc. Rev.* **2017**, *46*, 415-430. b) Fyfe, J. W. B.; Watson, A. J. B. *Chem.* **2017**, *3*, 31-55. c) Collins, B. S. L.; Wilson, C. M.; Myers, E. L.; Aggarwal, V. K. *Angew. Chem., Int. Ed.* **2017**, *56*, 11700-11733.

[118] Alfaro, R.; Parra, A.; Alemán, J; Ruano, J. L. G.; Tortosa, M. *J. Am. Chem. Soc.* **2012**, *134*, 15165-15168.

[119] For selected examples of copper-catalyzed carboborations of alkynes see: a) Liu, P.; Fukui, Y.; Tian, P.; He, Z. -T.; Sun, C. -Y.; Wu, N. -Y.; Lin, G. -Q. *J. Am. Chem. Soc.* **2013**, *135*, 11700−11703. b) Zhou, Y.; You, W.; Smith, B. K.; Brown, M. K. *Angew. Chem. Int. Ed.* **2014**, *53*, 3475−3479. c) Itoh, T.; Shimizu, Y.; Kanai, M. *J. Am. Chem. Soc.* **2016**, *138*, 7528−7531. d) Cheng, L. J.; Mankad, N. P. *Angew. Chem. Int. Ed.* **2018**, *57*, 10328-10332. For selected examples of copper-catalyzed carboborations of alkenes see: a) Ito, H.; Kosaka, Y.; Nonoyama, K.; Sasaki, Y.; Sawamura, M. *Angew. Chem. Int. Ed.* **2008**, *47*, 7424-7427. b) Zhong, C.; Kunii, S.; Kosaka, Y.; Sawamura, M.; Ito, H. *J. Am. Chem. Soc.* **2010**, *132*, 11440-11442. c) Meng, F.; McGrath, K. P.; Hoveyda, A. H. *Nature* **2014**, *513*, 367-374. d) Semba, K.; Nakao, Y. *J. Am. Chem. Soc.* **2014**, *136*, 7567-7570. e) Whyte, A.; Burton, K. I.; Zhang, J.; Lautens, M. *Angew. Chem. Int. Ed.* **2018**, *57*, 13927-13930. For selected examples of copper-catalyzed carboborations of allenes see: a) Meng, F.; Jang, H.; Jung, B.; Hoveyda, A. H. *Angew. Chem. Int. Ed.* **2013**, *52*, 5046-5051. b) Semba, K.; Bessho, N.; Fujihara, T.; Terao, J.; Tsuji, Y. *Angew. Chem. Int. Ed.* **2014**, *53*, 9007-9011. For selected examples of cooperative Cu/Pd catalyzed arylborations see: a) Semba, K.; Nakao, Y. *J. Am. Chem. Soc.* **2014**, *136*, 7567-7570. b) Logan, K. M.; Smith, K. B.; Brown, M. K. *Angew. Chem. Int. Ed.* **2015**, *54*, 5228-5231. c) Logan, K. M.; Brown, M. K. *Angew. Chem. Int. Ed.* **2017**, *56*, 851-855. d) Bergmann, A. M.; Dorn, S. K.; Smith, K. B.; Logan, K. M. *Angew. Chem. Int. Ed.* **2019**, *58*, 1719-1723.

cyclobutenes controlling the diastereo- and the enantioselectivity by choosing the appropriate catalytic system.

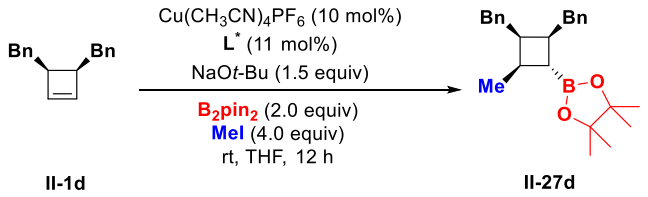


Scheme 2-51: Objectives of this section.

2.3.2. Screening of Conditions.

Intrigued by this result, we selected a set of chiral phosphines to test the feasibility of this reaction under our copper-catalyzed conditions. We tested different ligands and we found that Segphos derivatives, although best suited for the hydroboration, did not give good results in the carboboration reaction. The desired product **II-27d** was formed with poor yields and low enantioselectivities (**Table *2-4***, entries 2 to 4). Ferrocenyl type ligand **L5** did not give the desired product **II-27d** (**Table *2-4***, entry 5). Quinoline based ligand, QuinoxP* (**L6**), was the best performing ligand, forming cyclobutane **II-27d** with good yield, complete control of the diastereoselectivity and good enantioselectivity (**Table *2-4***, entry 6). The best performing ligand controlling the enantioselectivity was BenzP* (**Table *2-4***, entry 10), but unfortunately the yield was low. (*R*)-Difluorphos gave also good results (**Table *2-4***, entry 11), but QuinoxP* was superior.

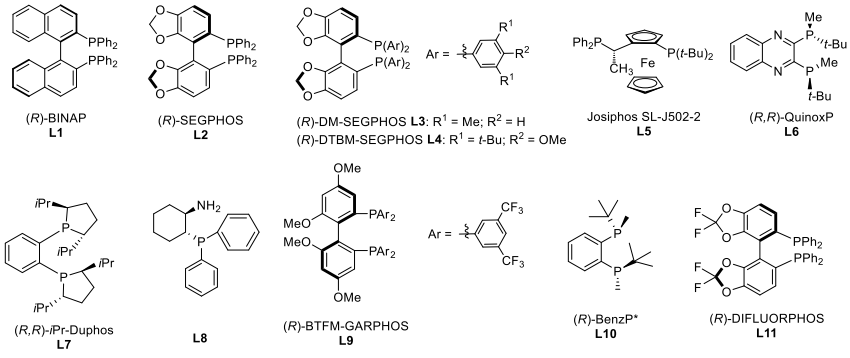
Table 2-4: Ligand Optimization.



II-1d **II-27d**

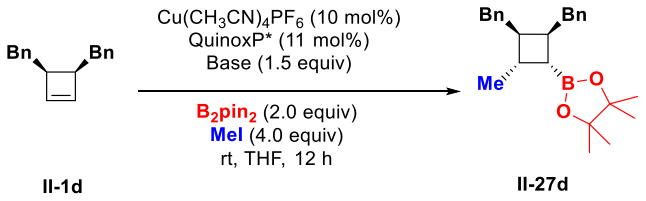
Entry	L*	d.r.[b]	e.r.[c]	Yield (%)[d]
1	**L1**	98:2	64:36	18
2	**L2**	>98:2	57:43	22
3	**L3**	95:5	59:41	12
4	**L4**	94:6	67:33	10
5	**L5**	-	-	<5
6	**L6**	**98:2**	**92:8**	**71**
7	**L7**	92:8	77:23	35
8	**L8**	98:2	82:18	8
10	**L10**	98:2	96:4	26
11	**L11**	98:2	88:12	47

[a] Reaction conditions: **II-1d** (0.2 mmol), B_2pin_2 (0.20 mmol), NaO*t*-Bu (1.5 equiv), $Cu(CH_3CN)_4PF_6$ (10 mol%), **L*** (11 mol%), MeI (0.8 mmol), THF (0.2 M). [b]d.r. determined by ^{1}H-NMR analysis. [c]e.r. determined by chiral SFC. [d] Yield of isolated **II-27d**.



With the optimal ligand in hand, we proceeded to the optimization of the base (**Table *2-5***). KO*t*-Bu afforded cyclobutylboronate **II-27d** with poor yield and the lower stereoselectivity (**Table *2-5***, entry 2). NaOMe did not provide the desired product in appreciable yield (**Table *2-5***, entry 3).

Table 2-5: Base Optimization.



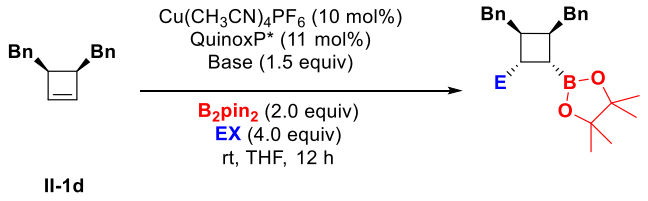
II-1d **II-27d**

Entry	Base	d.r.[b]	e.r.[c]	Yield (%)[d]
1	**NaO*t*-Bu**	**98:2**	**92:8**	**71**
2	KO*t*-Bu	95:5	82:18	17
3	NaOMe	-	-	<5

[a] Reaction conditions: **II-1d** (0.2 mmol), B_2pin_2 (0.20 mmol), Base (1.5 equiv), $Cu(CH_3CN)_4PF_6$ (10 mol%), QuinoxP* (11 mol%), MeI (0.8 mmol), THF (0.2 M). [b]d.r. determined by ^{1}H-NMR analysis. [c]e.r. determined by chiral SFC. [d] Yield of isolated **II-27d**.

We also tested different electrophiles to see the possible scope of the reaction (**Table *2-6***). Unfortunately, other electrophiles failed to form the desired product.

Table 2-6: Electrophile optimization.



Entry	Electrophile	d.r.[b]	e.r.[c]	Yield (%)[d]
1	**MeI**	**98:2**	**92:8**	**71**
2	MeOMs	-	-	<5
3	MeOTs	-	-	<5
4	MeOTf	-	-	<5
5	BnCl	-	-	<5
6	AllylI	-	-	<5

[a] Reaction conditions: **II-1d** (0.2 mmol), B_2pin_2 (0.20 mmol), Base (1.5 equiv), $Cu(CH_3CN)_4PF_6$ (10 mol%), QuinoxP* (11 mol%), EX (0.8 mmol), THF (0.2 M). [b]d.r. determined by ^{1}H-NMR analysis. [c]e.r. determined by chiral SFC. [d] Yield of isolated product.

2.3.3. Scope of the Reaction.

With the optimal condition in hand, we proceeded to test them with a variety of cyclobutenes (**Figure *2-8***).

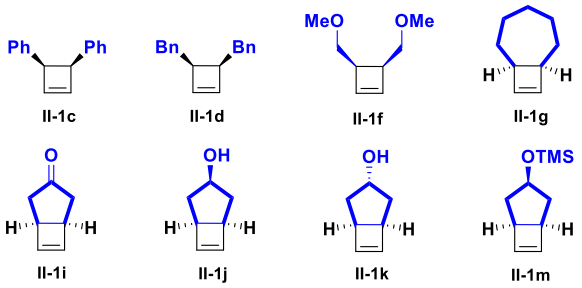
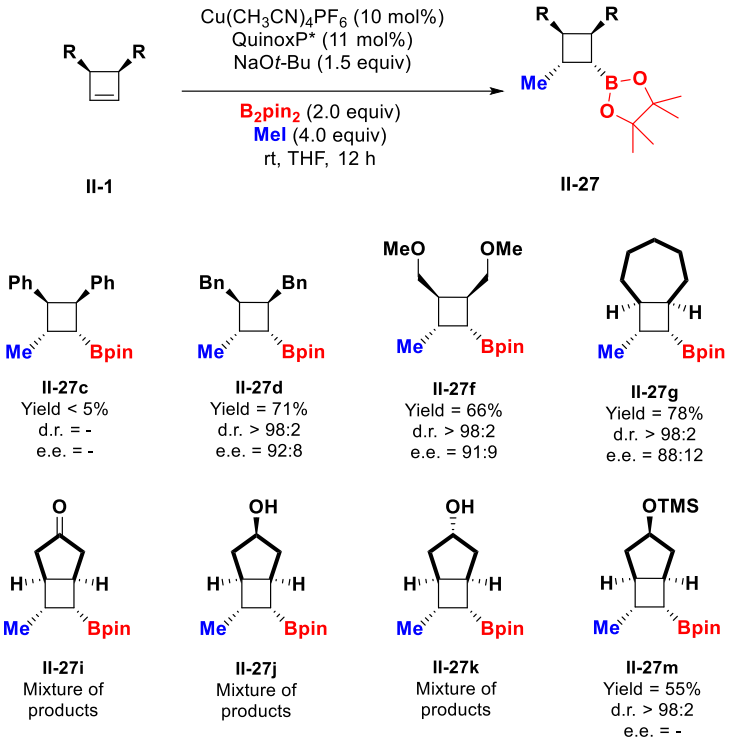


Figure 2-8: Disubstituted cyclobutenes.

When we applied the optimal condition to cyclobutene **II-1c**, we were surprised that the reaction did not give the desired product **II-27c**. Analysis of the ^{1}H-NMR concluded that under the carboboration conditions, cyclobutene **II-1c** is not stable, and it opened to the correspondent diene. Cyclobutene bearing an alkyl chain with alkoxy groups **II-1f** gave the desired product with good yield and stereoselectivities (66%, d.r. > 98:2; e.r. = 91:9). Methyl substituted cyclobutylboronate **II-27g** was obtained from bicyclic cyclobutene **II-1g** with excellent diastereoselectivity and slightly lower enantiocontrol (78%, d.r. > 98:2; e.r. = 88:12). When we tested cyclobutenes **II-1i**, **II-1j** and **II-1k** we obtained complicated mixtures of products. We reasoned that the ketone and the alcohols were interfering with the outcome of the reaction. We decided to protect cyclobutene **II-1j** with a silyl group, and we were happy to see that the correspondent cyclobutylboronate **II-27m** was formed in moderate yield and complete diastereoselectivity (55%). Unfortunately, the benzoylated product prepared through oxidation-protection of the C-B bond was not

stable under HPLC conditions and we obtained complicated chromatograms that did not allow us to measure the enantiomeric ratio of the product. Although the study of the scope is not complete, these preliminary results are a proof of concept to show that the enantioselective carboboration of cyclobutenes is a feasible transformation.

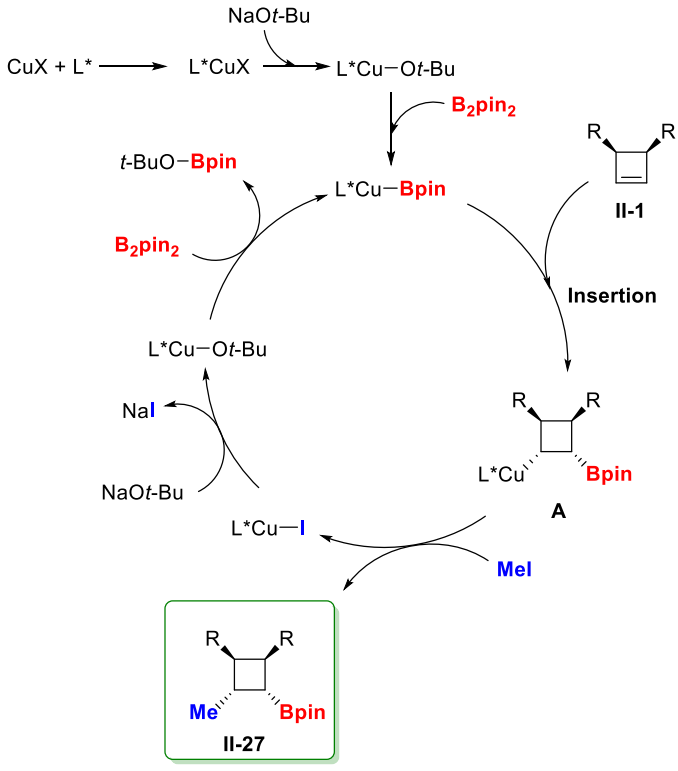


Scheme 2-52: Scope of the enantioselective carboboration of *meso*-cyclobutenes.

2.3.4. Mechanistic Proposal.

Although we do not have a model capable of explaining the differences observed between the carboboration and the hydroboration events, a plausible mechanism for the copper(I)-catalyzed carboboration of cyclobutenes is proposed in **Scheme *2-53***. First, the reaction of copper(I) salt, the ligand and sodium *tert*-butoxide formed a copper alkoxide. This alkoxide (L*Cu-O*t*Bu) could undergo a σ-bond metathesis reaction with bis(pinacolato)diboron to form a chiral copper-boryl complex (L*Cu-Bpin). Then, insertion of the cyclobutene into the copper-boryl complex would afford cyclobutyl copper intermediate **A**, being this the most plausible stereodetermining step of the borylation. Reaction with MeI, likely through an oxidative addition-reductive elimination sequence, would provide the carboboration product and copper-iodine (L*Cu-I) that would regenerate the catalytic cycle after reaction with another equivalent of the alkoxide. We cannot rule out the activation of the boron atom in intermediate **II-A** with the alkoxide to promote the formation of an "ate" complex, facilitating the C-C bond formation event, as proposed by Mauleón, Gómez-Arrayás and Carretero in the intramolecular carboboration of alkynes.[120]

[120] Kim-Lee, S. H.; Alonso, I.; Mauleon, P.; Gomez-Arrayas, R.; Carretero, J. C. *ACS Catal*. **2018**, *8*, 8993-9005.



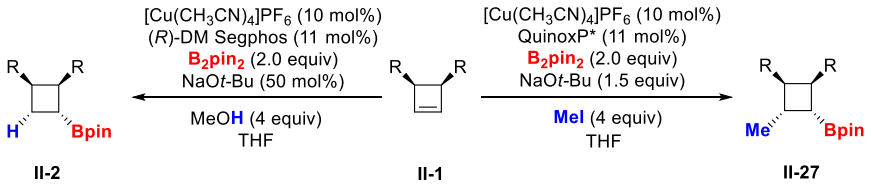
Scheme 2-53: Mechanism for the enantioselective carboboration of cyclobutenes.

2.4. Conclusions.

In this chapter we have described the diastero- and enantioselective copper-catalyzed hydroboration of *meso*-cyclobutenes. Our method represents the first catalytic enantioselective synthesis of cyclobutylboronates. Through a desymmetrization approach, functionalized cyclobutanes with up to four stereocenters have been prepared (**Scheme *2-54***).

A combination of a commercially available Segphos derivative along with an inexpensive copper(I) catalyst provided the enantiomerically enriched cyclobutylboronates in high yield and almost perfect sterocontrol. Further functionalization of the C-B bond gave access to different valuable intermediates.

Furthermore, we have also successfully trapped the cyclobutylcopper intermediate with methyl iodide, synthetizing cyclobutylboronates with four contiguous stereocenters. In this case, chiral ligand QuinoxP* afforded the best results.



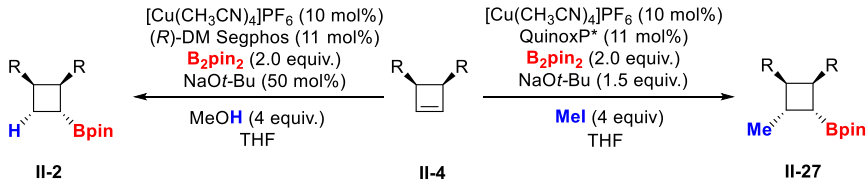
Scheme 2-54: Copper-catalyzed hydro- and carboboration of cyclobutenes.

2.5. Conclusiones.

En este capítulo, hemos descrito la primera hidroboración diastero- y enantioselectiva catalizada por cobre de ciclobutenos *meso*. Hemos sintetizado con éxito ciclobutilboronatos con hasta cuatro centros estereogénicos en la estructura siguiendo una estrategia de desimetrización (**Esquema *2-55***).

Utilizando una fosfina bidentada comercial de la familia Segphos y un catalizador de cobre(I), hemos preparado ciclobutilboronatos enantioméricamente enriquecidos con rendimientos elevados y excelente esterocontrol. El enlace C-B se ha derivatizado a través de distintas transformaciones para preparar importantes intermedios sintéticos.

Finalmente, hemos conseguido atrapar el intermedio de ciclobutilcobre con ioduro de metilo, preparando ciclobutilboronatos con cuatro centros estereogénicos contiguos. En este caso, el ligando quiral QuinoxP* proporcionó los mejores resultados.



Esquema 2-55: Hidro- y carboboración de ciclobutenos catalizada por cobre.

2.6. Supplementary Data.

2.6.1. General Experimental Details.

Tetrahydrofuran and dichloromethane were purified by passing through a Pure Solv™ column drying system from Innovative Technology, Inc. Additionally, THF and methanol were degassed through three consecutive freeze-pump-thaw cycles. Diethyl ether, chloroform, dimethoxyethane and ethyl acetate were dried using activated 4Å molecular sieves and stored under argon. Unless indicated otherwise, all reactions were conducted under an argon atmosphere using flame-dried glassware with standard vacuum-line techniques. NMR spectra were acquired on a Bruker 300 spectrometer, running at 300, and 75 MHz for ^{1}H and ^{13}C, respectively. Chemical shifts (δ) are reported in ppm relative to residual solvent signals ($CDCl_3$, 7.26 ppm for ^{1}H NMR and 77.2 ppm for ^{13}C NMR respectively). ^{13}C NMR spectra were acquired on a broad band decoupled mode. The following abbreviations are used to describe peak patterns when appropriate: s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), sex (sextet), sept (septuplet), m (multiplet), br (broad). Analytical thin layer chromatography (TLC) was performed using pre-coated aluminum-backed plates (Merck Kieselgel 60 F254) and visualized by ultraviolet irradiation or phosphomolybdic acid dip, potassium permanganate dip, vanillin dip or cerium ammonium molybdate dip. Purification of reaction mixtures was carried out by flash chromatography (FC) using silica gel Merck-60 or Florisil® 60-100 mesh from Aldrich. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. The enantiomeric ratio (er) of the products was determined by stationary phase SFC or UHPLC using chiral columns. Mass Spectrometry (MS) and High-Resolution Mass Spectrometry (HRMS) were registered in a spectrometer GCT Agilent Technologies 6890N using Electronic Impact (E.I.) techniques at 70 eV and electrospray (ESI^+ or ESI^-). Melting points were determined in a GallenKamp apparatus

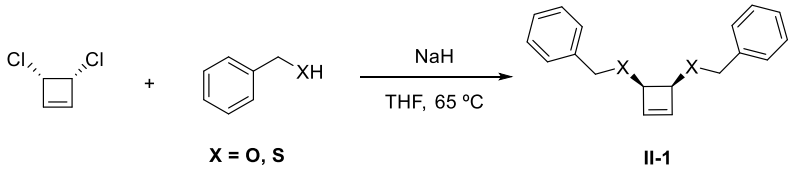
in open capillary tubes. All ligands, $[Cu(CH_3CN)_4]PF_6$ and NaO*t*-Bu (2.0 M solution in THF), were acquired from commercial sources and were used without further purification. Bis(pinacolato)diboron was recrystallized in *n*-pentane before used.

3,5-Cycloheptadienol was prepare following a reported procedure.[105]

2.6.2. Synthesis of Starting Materials.

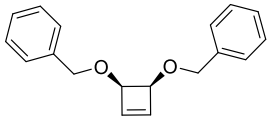
2.6.2.1. Synthesis of (3R,4S*)-3,4-bis(benzyloxy)cyclobut-1-ene, **II-1a** and (3R*,4S*)-3,4-bis(benzylthio)cyclobut-1-ene, **II-1b**.*

Compound **II-1a** and **II-1b** were prepared following a similar procedure reported in the bibliography.[101]



To an oven-dried flask was added NaH (2.24 equiv) and THF (0.25 M). The solution was vigorously stirred at 0 ºC and the correspondent nucleophile (5.25 equiv) was added dropwise to the mixture. It was stirred for 15 min and 3,4-dichlorocyclobut-1-ene (1 equiv) was added. It was stirred at 65 ºC for 12 h. The reaction was cool down at room temperature and water was added. To the solution was added ether and the phases were separated. Aqueous phase was extracted with ether (x2). The combined organic phases were dried over $MgSO_4$ and the solvent removed under reduced pressure. Crude was purified by flash column chromatography using hexanes/ethyl acetate 95:5 as eluent.

(3*R**,4*S**)-3,4-bis(Benzyloxy)cyclobut-1-ene, **II-1a**.

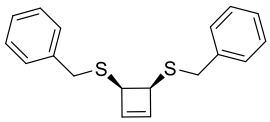


II-1a

From 3,4-dichlorocyclobut-1-ene (0.768 g, 6.3 mmol), following the general procedure described above, compound **II-1a** (1.0 g, 3.8 mmol) was obtained in 60% yield as yellow oil.

^{1}H-NMR, **^{13}C-NMR** and **MS** data were consistent with literature values.[101] **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 7.30 (t, *J* = 6.8 Hz, 4H), 7.27 – 7.21 (m, 4H), 7.21 – 7.16 (m, *J* = 3.7 Hz, 2H), 6.34 – 6.28 (m, 2H), 4.70 (dd, *J* = 33.8, 11.6 Hz, 6H), 4.68 – 4.67 (m, 2H).

(3R*,4S*)-3,4-bis(Benzylthio)cyclobut-1-ene, **II-1b**.



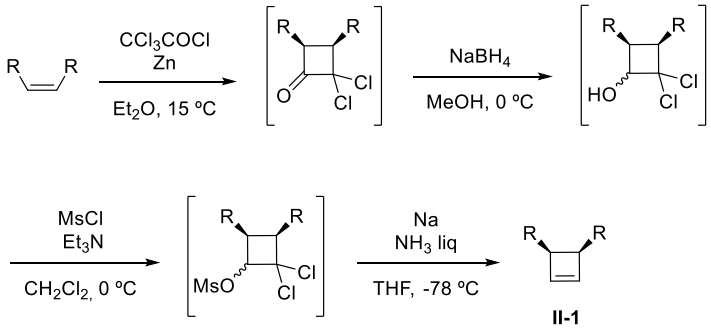
II-1b

From 3,4-dichlorocyclobut-1-ene (0.500 g, 4.06 mmol), following the general procedure described above, compound **II-1b** (0.8 g, 2.7 mmol) was obtained in 66% yield as yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.31 – 7.23 (m, 10H), 5.87 (s, 2H), 4.06 (s, 2H), 3.79 (d, *J* = 3.5 Hz, 4H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 138.7, 138.6, 129.2, 128.6, 127.0, 52.2, 36.2. **HRMS-ESI^{+}** m/z calculated for $C_{18}H_{18}S_2Na$ $[M+Na]^+$: 321.0742, found 321.0731.

*2.6.2.2. General procedure for synthesis of cyclobutenes **II-1d**, **II-1f**, **II-1g**, **II-1h**.*

Compounds **II-1d**, **II-1f**, **II-1g** and **II-1h** were prepared following a similar procedure reported in the bibliography.[102]



To a mixture of activated zinc (2 equiv), the corresponding *cis*-alkene (1 equiv), and anhydrous ether (2.5 mL/mmol of alkene), placed in a sonication bath maintained at 15-20 °C, was added a solution of trichloroacetyl chloride (1.44 equiv) in ether (1.2 mL/mmol of alkene) over a 90 min period. Sonication of the reaction mixture at 15 °C was continued for another 6.5 h. The mixture was quenched with wet ether and filtered through a sintered glass funnel; the zinc was rinsed with wet ether, and the total filtrate was washed with water (x2), $NaHCO_3$ (aq) (x5), and brine. The organic phase was dried over $MgSO_4$ and the solvent removed under reduced pressure. The crude product was used in the next step without further purification.

The corresponding dichloroketone (1 equiv) and methanol (5 mL/mmol of dichloroketone) were cooled to 0 ºC and sodium borohydride (2.5 equiv) was added portionwise over 2 h. The reaction mixture was allowed to warm

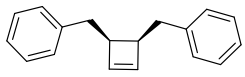
to room temperature and was stirred for 2 h, and then it was re-cooled to 0 ºC and diluted with a cold mixture of NH_4Cl (aq) and ether. The layers were separated, and the aqueous phase was extracted with ether (x3). The ethereal extract was washed with saturated solution of $NaHCO_3$, water, and brine, and then it was dried over $MgSO_4$ and filtered. Concentration afforded the crude product, which was used in the next step without further purification.

A solution of the corresponding alcohol (1 equiv) in CH_2Cl_2 (2.3 mL/mmol of alcohol) was cooled to 0 ºC, and then triethylamine (4.5 equiv) was added. Methanesulfonyl chloride (3.5 equiv) was placed in an addition funnel and added slowly over 1.5 h. The bath ice was allowed to melt, thus allowing the reaction mixture to slowly warm to room temperature. After being stirred for 3 h, the reaction mixture was again cooled to 0 ºC for work-up. A mixture of cold water (2.3 mL/mmol of alcohol) and CH_2Cl_2 (2.3 mL/mmol of alcohol) was added to the reaction mixture. It was stirred for 30 min and cold 1N HCl was added to acidify the mixture. The layers were separated, and the aqueous phase was extracted three times with CH_2Cl_2. The organic extract was washed twice with cold water, twice with cold 1N HCl, and with a saturated solution of $NaHCO_3$ and brine, and then dried over $MgSO_4$, and filtered. The resulting dark orange solution was concentrated by rotary evaporation, affording a dark orange liquid. This crude mesylate was used without further purification in the synthetic transformation that follows.

Ammonia (24 mL/mmol of mesylate) was condensed at -78 ºC in a three-necked flask fitted with a magnetic stirrer, a dry ice/acetone condenser, and an addition funnel. Sodium (15 equiv) was added in small pieces, producing a deep blue color as cooling was maintained at -78 ºC. A solution of crude dichloro mesylate (1 equiv) in dry tetrahydrofuran (4.5 mL/mmol of mesylate) was placed in the addition funnel and added to the

Na/NH_3 over 30 min, and then the reaction mixture was allowed to warm to -40 to -35 ºC and stirred for 2 h. To destroy the excess sodium, NH_4Cl was added until the blue color was gone. The dry ice/acetone condenser and the addition funnel were removed. The reaction mixture was slowly allowed to warm to 0 ºC, allowing the NH_3 to evaporate. Water (12 mL/mmol of mesylate) was added to dissolve the remaining salts and then, pentane (4 mL/mmol of mesylate) was added. The layers were separated, and the aqueous phase was extracted three times with pentane. The pentane extract was washed with water, 1N HCl, water, saturated $NaHCO_3$, water, and brine. The organic phase was dried over $MgSO_4$ and the solvent removed under reduced pressure. Crude was purified by flash column chromatography over silica gel using *n*-pentane as eluent.

(3*R**,4*S**)-3,4-Dibenzylcyclobut-1-ene, **II-1d**.

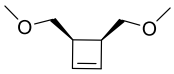


II-1d

From (*Z*)-1,4-diphenylbut-2-ene (2 g, 9.6 mmol), following the general procedure described above, compound **II-1d** (0.35 g, 1.5 mmol) was obtained in 16% overall yield (4 steps) as an orange oil.

^{1}H RMN (300 MHz, $CDCl_3$): δ 7.42 – 7.35 (m, 4H), 7.32 – 7.25 (m, 6H), 6.23 (s, 2H), 3.41 – 3.28 (m, 2H), 3.01 (dd, *J* = 13.5, 5.6 Hz, 2H), 2.82 (dd, *J* = 13.4, 10.5 Hz, 2H). **^{13}C RMN** (75 MHz, $CDCl_3$): δ 141.2, 139.7, 128.8, 128.4, 125.8, 47.7, 36.5. **HRMS-EI$^+$** m/z calculated for $C_{18}H_{18}$ $[M]^+$: 234.1409, found 234.1407.

(3*R**,4*S**)-3,4-bis(Methoxymethyl)cyclobut-1-ene, **II-1f**.

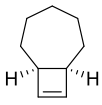


II-1f

From (*Z*)-1,4-dimethoxybut-2-ene (4 g, 34.5 mmol), following the general procedure described above, compound **II-1f** (1.3 g, 9.2 mmol) was obtained in 27% overall yield (4 steps) as a colorless oil after a flash column chromatography over silica gel using n-pentane/ethyl ether 80:20 as eluent.

^{1}H RMN (300 MHz, $CDCl_3$): δ 6.16 (s, 2H), 3.58 – 3.50 (m, 2H), 3.50 – 3.42 (m, 2H), 3.33 (s, 6H), 3.22 – 3.14 (m, 2H). **^{13}C RMN** (75 MHz, $CDCl_3$): δ 138.6, 72.9, 58.9, 45.7. **HRMS-EI^{+}** m/z calculated for $C_8H_{14}O_2$ $[M]^{+}$: 142.0994, found 142.0995.

(1*R**,7*S**)-Bicyclo[5.2.0]non-8-ene, **II-1g**.

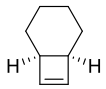


II-1g

From cycloheptene (4 g, 41.6 mmol), following the general procedure described above, compound **II-1g** (1.44 g, 11.8 mmol) was obtained in 28% yield overall yield (4 steps) as a colorless oil.

^{1}H RMN (300 MHz, $CDCl_3$): δ 6.07 (s, 2H), 2.97 – 2.86 (m, 2H), 1.82 – 1.71 (m, 5H), 1.44 – 1.15 (m, 5H). **^{13}C RMN** (75 MHz, $CDCl_3$): δ 139.7, 48.9, 32.3, 30.7, 28.5. **HRMS-EI^{+}** m/z calculated for C_9H_{14} $[M]^{+}$: 122.1096, found 122.1098.

(1*R**,6*S**)-Bicyclo[4.2.0]oct-7-ene, **II-1h**.



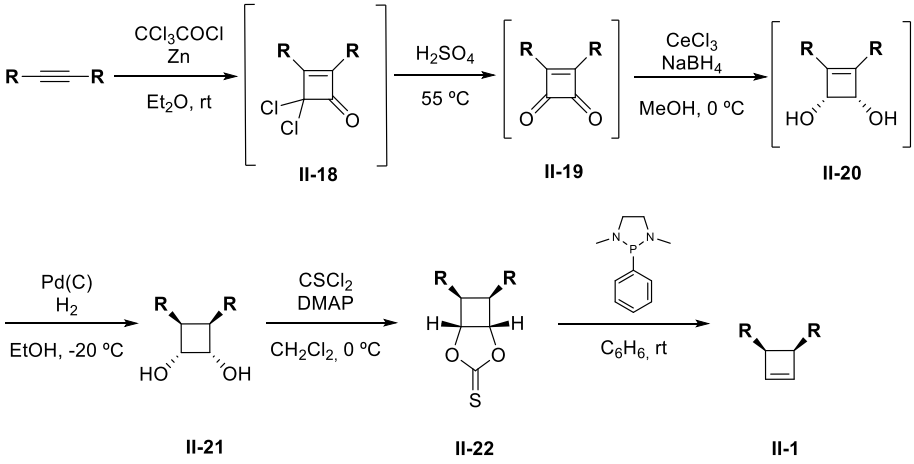
II-1h

From cycloheptene (5 g, 59.4 mmol), following the general procedure described above, compound **II-1h** (1.41 g, 13 mmol) was obtained in 22% yield overall yield (4 steps) as a colorless oil.

^{1}H-NMR, **^{13}C-NMR** and **MS** data were consistent with literature values.[102] **^{1}H RMN** (300 MHz, $CDCl_3$): δ 6.17 (s, 2H), 2.89 (dd, *J* = 8.3, 4.1 Hz, 2H), 1.80 – 1.63 (m, 4H), 1.48 – 1.38 (m, 2H), 1.38 – 1.27 (m, 2H).

2.6.2.3. Synthesis of (3R,4S*)-3,4-diphenylcyclobut-1-ene, **II-1c** and (3R*,4S*)-3,4-dipropylcyclobut-1-ene, **II-1e**.*

Compounds **II-1c** and **II-1e** were prepared by following a similar reported procedure in the bibliography.[103]



To a suspension of activated Zn (3.0 equiv.) in anhydrous ether (0.15 M) was added alkyne (1.0 equiv). Later, trichloroacetyl chloride (1.3 equiv), dissolved in dimethoxyethane (2 M), was added dropwise with vigorous agitation. The mixture was stirred at room temperature for 36 h. The reaction mixture was filtered over celite and washed with saturated $NaHCO_3$ (x3) and saturated NaCl (x3). The organic phase was dried over $MgSO_4$ and the solvent removed under reduced pressure. The reaction crude was used without further purification in the next step.

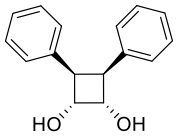
To concentrated H_2SO_4 (2 mL/mmol X) at 55 ºC, was added **II-18** (1 equiv). The solution was stirred for 12 min, and then quenched with ice. The solution was extracted with ether (x3) and the combined organic phases were washed with saturated $NaHCO_3$ (x3) and saturated NaCl (x3). The organic phase was dried over $MgSO_4$ and the solvent removed under reduced pressure. The reaction crude was used without further purification in the next step.

To a solution of **II-19** (1 equiv) in methanol (0.05M) was added cerium trichloride heptahidrate (2.2 equiv) and the solution was vigorously stirred at 0 ºC for 15 min. Sodium borohydride (2.7 equiv) was added in small portions and the mixture was stirred at 0 ºC until full conversion by TLC (2 h). The reaction was quenched with saturated NH_4Cl and the aqueous phase was extracted with AcOEt (x10). The combined organic phases were dried over $MgSO_4$ and the solvent removed under reduced pressure. The resulting diol was used without further purification in the next step.

A mixture of diol **II-20** (1 equiv) and Pd(C) (0.1 equiv) in ethanol (0.2 M) was vigorously stirred under a hydrogen atmosphere at -20 ºC until full conversion by TLC (2 h). The reaction mixture was filtered over celite® and the solvent was removed under reduced pressure. The reaction crude was

purified by flash column chromatography using cyclohexane/ethyl acetate 50:50 as eluent.

(1*R**,2*S**,3*S**,4*R**)-3,4-Diphenylcyclobutane-1,2-diol, **II-21c**.

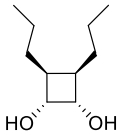


II-21c

From diphenylacetilene (2.2 g, 12.1 mmol), following the general procedure described above, compound **II-21c** (0.931 mg, 3.9 mmol) was obtained in 32% yield overall yield (4 steps) as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.16 – 7.01 (m, 6H), 6.89 (d, *J* = 7.8 Hz, 4H), 4.70 (s, 2H), 3.92 (d, *J* = 3.3 Hz, 2H), 3.14 – 2.91 (m, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 138.5, 128.2, 126.2, 71.6, 51.1. **mp** = 144-145 ºC.

(1*R**,2*S**,3*R**,4*S**)-3,4-Dipropylcyclobutane-1,2-diol, **II-21e**.



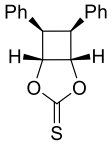
II-21e

From 4-octyne (860 mg, 7.8 mmol), following the general procedure described above, compound **II-21e** (375 mg, 2.18 mmol) was obtained in 28% yield overall yield (4 steps) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 3.90 (d, *J* = 2.8 Hz, 2H), 2.31 (s, 2H), 2.17 (br, 2H), 1.46 – 1.34 (m, 4H), 1.34 – 1.24 (m, 4H), 0.92 (m, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 72.5, 43.4, 30.6, 21.2, 14.4. **mp** = 56 - 57 ºC. **HRMS-EI^{+}** m/z calculated for $C_{10}H_{16}O_2$ $[M-4H]^{+}$: 168.1150, found 168.1157.

To a solution of **II-21** (1 equiv) and DMAP (2.45 equiv) in anhydrous CH_2Cl_2 (0.2M) at 0 ºC was added dropwise thiophosgene (1.2 equiv). The mixture was vigorously stirred at 0 ºC until full conversion by TLC (2 h). The reaction was quenched adding silica gel and the reaction crude was purified by flash column chromatography over Florisil® using hexanes/ethyl acetate 90:10 as eluent.

(1*R**,5*S**,6*S**,7*R**)-6,7-Diphenyl-2,4-dioxabicyclo[3.2.0]heptane-3-thione, **II-22c**.

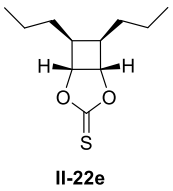


II-22c

From diol **II-21c** (956 mg, 4.0 mmol), following the general procedure described above, compound **II-22c** (880 mg, 3.1 mmol) was obtained in 80% yield as yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20 – 7.08 (m, 6H), 6.85 (d, *J* = 7.8 Hz, 4H), 5.60 (d, *J* = 1.6 Hz, 2H), 4.45 (s, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 192.5, 135.2, 128.6, 127.9, 127.2, 83.8, 50.5.

(1*R**,5*S**,6*R**,7*S**)-6,7-Dipropyl-2,4-dioxabicyclo[3.2.0]heptane-3-thione, **II-22e**.



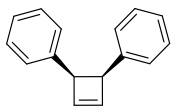
II-22e

From diol **II-21e** (750 mg, 4.4 mmol), following the general procedure described above, compound **II-22e** (0867 mg, 4 mmol) was obtained in 93% yield as yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 4.89 – 4.80 (s, 2H), 2.80 – 2.66 (m, 2H), 1.47 – 1.26 (m, 8H), 0.93 (t, *J* = 7.0 Hz, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 193.4, 84.6, 43.4, 29.2, 20.5, 14.0. **HRMS-EI$^+$** m/z calculated for $C_{11}H_{18}O_2S$ $[M]^+$: 214.1028, found 214.1037.

To a solution of tiocarbonate **II-22** (1 equiv) in benzene (0.5 M) at room temperature, Corey-Hopkins reagent (3 equiv) was added. The mixture was vigorously stirred at room temperature until full conversion by TLC (4-6h). Crude was purified by flash column chromatography using *n*-pentane as eluent.

(3*R**,4*S**)-3,4-Dipropylcyclobut-1-ene, **II-1c**.

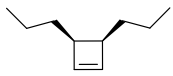


II-1c

From compound **II-22c** (1.0 g, 3.5 mmol), following the general procedure described above, compound **II-1c** (430 mg, 2.1 mmol) was obtained in 60% yield as colorless oil.

^{1}H-NMR, **^{13}C-NMR** and **MS** data were consistent with literature values.[121] **^{1}H RMN** (300 MHz, CDCl3) δ 7.04 – 6.87 (m, 10H), 6.53 (s, 2H), 4.51 (s, 2H).

(3*R**,4*S**)-3,4-Dipropylcyclobut-1-ene, **II-1e**.



II-1e

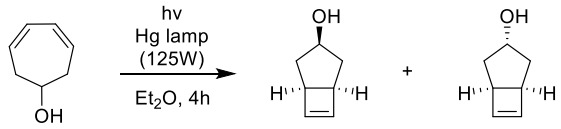
From compound **II-22e** (400 mg, 1.9 mmol), following the general procedure described above, compound **II-1e** (135 mg, 1.0 mmol) was obtained in 52% yield as colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.17 (s, 2H), 2.89 – 2.76 (m, 2H), 1.53 – 1.35 (m, 4H), 1.34 – 1.28 (m, 4H), 0.92 (t, *J* = 7.0 Hz, 6H).**^{13}C NMR** (75 MHz, $CDCl_3$): δ 140.2, 46.8, 32.3, 21.6, 14.5. **HRMS-EI^{+}** m/z calculated for $C_{10}H_{18}$ $[M]^{+}$: 138.1409, found 138.1410.

[121] Miyashi, T.; Wakamatsu, K.; Akiya, T.; Kikuchi, K.; Mukai, T. *J. Am. Chem. Soc.*, **1987**, *109*, 5270-5271.

2.6.2.4. Synthesis of (1R,3s,5S*)-bicyclo[3.2.0]hept-6-en-3-ol, **II-1j** and (1R*,3r,5S*)-bicyclo[3.2.0]hept-6-en-3-ol, **II-1k.***

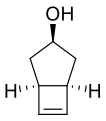
Compounds **II-1j** and **II-1k** were prepared by following a similar procedure reported in the bibliography.[105]



II-1j **II-1k**

A solution of 3,5-cycloheptadienol (2.2 g, 20.0 mmol) in anhydrous ether (800 mL) was bubbled with nitrogen for 30 min and then irradiated for 4 h with a quartz jacketed Hanovia immersion lamp. The solvent was removed under reduced pressure affording a mixture of both *endo* and *exo* bicyclo[3.2.0]hept-6-en-3-ol with a ratio of 2:1 (based on ^{1}H NMR analysis). The reaction crude was purified by flash column chromatography using cyclohexane/ethyl acetate 80:20 as eluent.

(1*R**,3*s*,5*S**)-Bicyclo[3.2.0]hept-6-en-3-ol, **II-1j.**

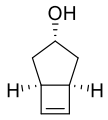


II-1j

From 3,5-cycloheptadienol (2.2 g, 20 mmol), following the general procedure described above, compound **II-1j** (580 mg, 5.3 mmol) was obtained in 26% yield as colorless oil.

^{1}H-NMR, **^{13}C-NMR** and **MS** data were consistent with literature values.[105] **^{1}H RMN** (300 MHz, $CDCl_3$) δ 6.33-6.35 (d, 2H), 4.25-4.36 (m, 1H), 3.30-3.35 (d, 2H), 1.95-2 (m, 2H), 1.70-1.75 (m, 2H).

(1*R**,3*r*,5*S**)-Bicyclo[3.2.0]hept-6-en-3-ol, **II-1k.**



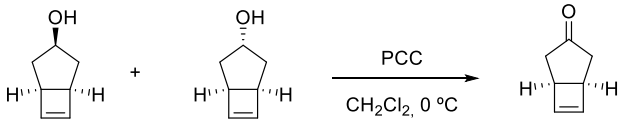
II-1k

From 3,5-cycloheptadienol (2.2 g, 20 mmol), following the general procedure described above, compound **II-1k** (650 mg, 5.9 mmol) was obtained in 30% yield as colorless oil.

^{1}H-NMR, **^{13}C-NMR** and **MS** data were consistent with literature values.[105] **^{1}H RMN** (300 MHz, $CDCl_3$) δ 5.94-5.92 (s, 2H), 4.42-4.38 (m,1H), 3.26-3.24 (m, 2H), 1.35-1.2 (m, 4H).

2.6.2.5. Synthesis of (1R,5S*)-bicyclo[3.2.0]hept-6-en-3-one, **II-1i.***

Compound **II-1i** was prepared by following a similar procedure reported in the bibliography.[105]

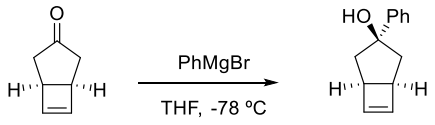


II-1j **II-1k** **II-i**

To a suspension of pyridinium chlorochromate (2.5 g, 11.0 mmol, 1.1 equiv) in CH_2Cl_2 (12 mL) at 0 ºC was added a solution of the above mixture of endo and exobicyclo[3.2.0]hept-6-en-3-ol dissolved in CH_2Cl_2 (7 mL). After 2 h stirring at room temperature, the supernatant liquid was poured into ether (50 mL) and the residual in the flask was extracted with ether (2 × 20 mL). The combined organic phases were filtered over a pad of silica and rinsed with ether. The solvent was removed under reduced pressure and the crude product was purified by distillation (75 ºC, 14 mbar).

^{1}H-NMR, **^{13}C-NMR** and **MS** data were consistent with literature values.[105] **^{1}H RMN** (300 MHz, CDCl3) δ 6.10 (s, 2 H), 3.47 (d, *J* = 7.6 Hz, 2 H), 2.35–2.41 (m, 2 H), 2.15–2.23 (m, 2 H).

2.6.2.6. Synthesis of (1R,3S*,5S*)-3-phenylbicyclo[3.2.0]hept-6-en-3-ol, **II-1l**.*

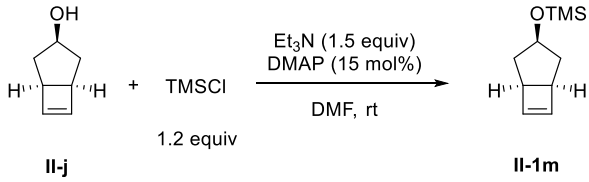


II-i **II-1l**

To a solution of **II-1i** (0.4 g, 3.7 mmol, 1 equiv) in THF (1.8 mL/mmol ketone), phenylmagnesium bromide (1.34 g, 7.4 mmol, 2 equiv) was added at -78 ºC. The mixture was stirred vigorously at -78 ºC until full conversion by TLC (4 h). The solution was extracted with AcOEt (x3) and the combined organic phases were washed with saturated NaCl (x3). The organic phase was dried over $MgSO_4$ and the solvent removed under reduced pressure. Crude was purified by flash column chromatography using *hexanes*/ethyl acetate 80:20 as eluent. Compound **II-1l** (0.214 g, 1.15 mmol) was obtained in 31% yield as colorless oil.

^{1}H RMN (300 MHz, $CDCl_3$): δ 7.48 (d, *J* = 7.8 Hz, 2H), 7.35 (t, *J* = 7.8 Hz, 2H), 7.23 (d, *J* = 7.8 Hz, 1H), 6.47 (d, *J* = 0.7 Hz, 2H), 3.57 (d, *J* = 7.1 Hz, 2H), 2.89 (s, 1H), 2.21 (d, *J* = 14.2 Hz, 2H), 2.10 (dd, *J* = 14.2, 7.1 Hz, 2H). **^{13}C RMN** (75 MHz, $CDCl_3$): δ 146.5, 144.2, 128.2, 126.7, 125.2, 86.8, 49.3, 44.3. **HRMS-ESI^{+}** m/z calculated for $C_{13}H_{14}ONa$ $[M+Na]^{+}$: 209.0936, found 209.0938.

2.6.2.7. Synthesis of (((1R,3s,5S)-bicyclo[3.2.0]hept-6-en-3-yl)oxy) trimethylsilane.

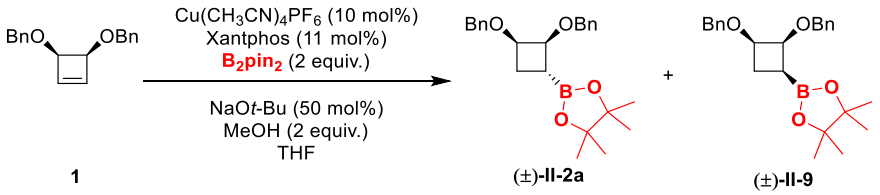


II-j **II-1m**

To a solution of **II-1j** (283 mg, 2.57 mmol, 1 equiv), DMAP (47 mg, 0.38 mmol, 0.15 equiv) and triethylamine (290 mg, 3.85 mmol, 1.5 equiv) in DMF (1 mL) was added TMSCl (328, 3.1 mmol, 1.2 equiv) at room temperature. The reaction mixture was stirred at room temperature until full conversion is observed by TLC (1 h). Et_2O and water were added, and the layers were separated. The combined organic phases were washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuum. Solvent was removed under reduced pressure and crude was purified by flash column chromatography over silica gel using *n*-hexanes/ethyl ether 95:5 as eluent. Compound **II-1m** (228 mg, 1.25 mmol) was obtained in 49% yield as colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 6.10 (s, 2 H,), 4.47-4.33 (m, 1 H), 3.24–3.16 (m, 2 H), 1.82-1.55 (m, 4 H), 0.08 (s, 9H). **^{13}C-NMR** (75 MHz, $CDCl_3$) δ 141.4, 78.9, 47.2, 37.7, 0.4. **HRMS-ESI$^+$** m/z calculated for $C_{13}H_{14}ONa$ $[M+Na]^+$: 209.0936, found 209.0938.

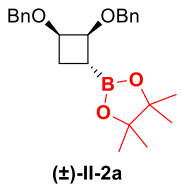
2.6.3. General procedure for synthesis of racemic cyclobutylboronates.



An oven-dried vial was charged with $[Cu(CH_3CN)_4]PF_6$ (7.5 mg, 0.02 mmol, 10.0 mol%), Xantphos (0.022 mmol, 11.0 mol%) and B_2pin_2 (2 equiv) and sealed with a septum. The vial was connected to an argon-vacuum line, evacuated and backfilled with argon (x3). THF (1 mL) was added and the mixture was stirred for 15 min at room temperature. A 0.2 M NaO*t*-Bu solution in THF (50 µL, 0.1 mmol, 0.5 equiv) was then added dropwise and the dark brown solution was stirred for 10 min. The reaction mixture was cooled at –78 °C for 10 min and cyclobutene **II-1a** (0.2 mmol, 1.0 equiv) was added followed by methanol (16 µL, 0.4 mmol, 2.0 equiv). Then, the reaction mixture was stirred overnight (16 h) at room temperature. Hexanes was added to the mixture and solvent was removed under reduced pressure. Crude was purified by flash column chromatography using n-hexane/ether 80:20 as eluent.

(±)-2-((1*R*,2*S*,3*R*)-2,3-bis(Benzyloxy)cyclobutyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, **(±)-II-2a**.

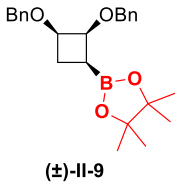
From **II-1a** (53.2 mg, 0.2 mmol), following the general procedure described above, compound (±)-**II-2a** (26 mg, 0.066 mmol) was obtained in 33% yield as colorless oil.



(±)-II-2a

^{1}H RMN (500 MHz, $CDCl_3$) δ 7.30 (d, *J* = 7.3 Hz, 2H), 7.28 (s, 2H), 7.24 (t, *J* = 7.3 Hz, 4H), 7.18 (t, *J* = 7.1 Hz, 2H), 4.57 – 4.42 (m, 4H), 4.12 – 4.06 (m, 2H), 2.26 – 2.10 (m, 1H), 1.98 – 1.90 (m, 2H), 1.15 (s, 6H), 1.15 (s, 6H).**^{13}C RMN** (126 MHz, $CDCl_3$) δ 138.8, 138.8, 128.4, 128.3, 127.9, 127.9, 127.5, 127.5, 83.4, 77.5, 75.6, 71.0, 70.6, 26.9, 24.9, 24.8. [note: the carbon attached to boron was not observed due to quadrupole broadening caused by the ^{11}B nucleus]. **HRMS-EI^{+}** m/z calculated for $C_{23}H_{28}BO_4$ $[M\text{-}CH_3]^{+}$: 379.2081, found 379.2078.

(±)-2-[(1*R*,2*R*,3*S*)-2,3-bis(Benciloxi)ciclobutil]-4,4,5,5-tetrametil-1,3,2-dioxaborolano, **(±)-II-9**.

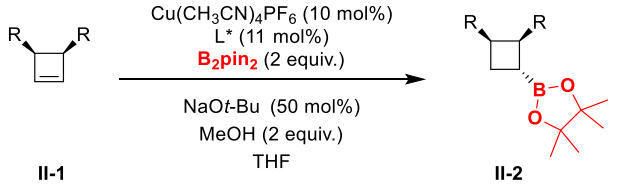


(±)-II-9

From **II-1a** (53.2 mg, 0.2 mmol), following the general procedure described above, compound (±)-**II-9** (4.7 mg, 0.012 mmol) was obtained in 6% yield as colorless oil.

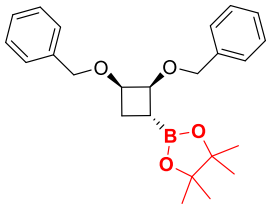
^{1}H RMN (500 MHz, $CDCl_3$) δ 7.41 – 7.38 (m, 2H), 7.34 – 7.29 (m, 6H), 7.27 – 7.23 (m, 2H), 4.76 (d, *J* = 12.2 Hz, 1H), 4.62 (d, *J* = 12.2 Hz, 1H), 4.53 – 4.46 (m, 2H), 4.39 – 4.35 (m, 1H), 4.03 (dd, *J* = 10.9, 8.2 Hz, 1H), 2.25 – 2.16 (m, 1H), 1.75 – 1.67 (m, 1H), 1.22 (s, 6H), 1.22 (s, 6H). **^{13}C RMN** (126 MHz, $CDCl_3$) δ 139.4, 138.8, 128.4, 128.2, 127.7, 127.7, 127.5, 127.2, 83.5, 80.3, 74.5, 72.1, 70.2, 29.3, 25.1, 25.0. [note: the carbon attached to boron was not observed due to quadrupole broadening caused by the ^{11}B nucleus].

2.6.4. General procedure for the synthesis of chiral cyclobutylboronates **II-2**.



An oven-dried vial was charged with $[Cu(CH_3CN)_4]PF_6$ (7.5 mg, 0.02 mmol, 10.0 mol%) and ligand ((*R*)-DTBM-Segphos or (*R*)-DM-Segphos) (0.022 mmol, 11.0 mol%) and sealed with a septum. The vial was connected to an argon-vacuum line, evacuated and backfilled with argon (x3). THF (0.7 mL) was added and the mixture was stirred for 15 min at room temperature. With the vial still connected to the double line, the solvent was removed to dryness. Then, a solution of B_2pin_2 (2 equiv) in THF (1 mL) was added and the mixture was stirred for 15 min. A 0.2 M NaO*t*-Bu solution in THF (50 µL, 0.1 mmol, 0.5 equiv) was then added dropwise and the dark brown solution was stirred for 10 min. The reaction mixture was cooled at –78 °C for 10 min and the corresponding cyclobutene **II-1** (0.2 mmol, 1.0 equiv) was added followed by methanol (16 µL, 0.4 mmol, 2.0 equiv). Then, the reaction mixture was stirred overnight (16 h) at the optimal temperature for each case (–20 or 0 ºC). Hexanes was added to the mixture and solvent was removed under reduced pressure. Crude was purified by flash column chromatography over Florisil® (Eluent is indicated in each case).

(–)-2-[(1*R*,2*S*,3*R*)-2,3-bis(Benzyloxy)cyclobutyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, **II-2a**.

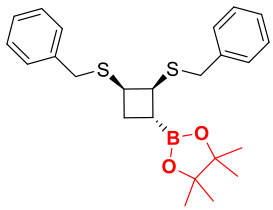


II-2a

From **II-1a** (53.2 mg, 0.2 mmol), following the general procedure described above ((*R*)-DM-Segphos, 0 °C) and purifying crude by flash column chromatography over Florisil® using *n*-pentane/ethyl ether 65:35 as eluent, compound **II-2a** (75.6 mg, 0.192 mmol) was obtained in 96% yield as a colorless oil.

Compound **II-2a** was obtained with a 99:1 enantiomeric ratio determined by SFC using Chiralpak-ID column [CO_2/MeOH (90:10)], 1.0 mL/min, τ_{major}= 8.8 min, τ_{minor}= 9.7 min. **[α]$^{20}_D$**= –15.0 (*c* = 1.0, $CHCl_3$). **^{1}H RMN** (500 MHz, $CDCl_3$): δ 7.32 – 7.27 (m, 4H), 7.24 (t, *J* = 7.3 Hz, 4H), 7.20 – 7.16 (m, 2H), 4.57 – 4.42 (m, 4H), 4.12 – 4.06 (m, 2H), 2.22 – 2.13 (m, 1H), 1.97 – 1.90 (m, 2H), 1.15 (s, 6H), 1.15 (s, 6H).**^{13}C RMN** (126 MHz, $CDCl_3$): δ 138.8, 138.8, 128.4, 128.3, 127.9, 127.9, 127.5, 127.5, 83.4, 77.5, 75.6, 71.0, 70.6, 26.9, 24.9, 24.8. [note: the carbon attached to boron was not observed due to quadrupole broadening caused by the ^{11}B nucleus]. **HRMS-EI$^+$** m/z calculated for $C_{23}H_{28}BO_4$ [M-CH_3]$^+$: 379.2081, found 379.2078.

(–)-2-[(1*R*,2*S*,3*R*)-2,3-bis(Benzylthio)cyclobutyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, **II-2b**.

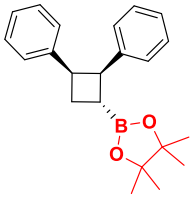


II-2b

From **II-1b** (59.6 mg, 0.2 mmol), following the general procedure described above ((*R*)-DTBM-Segphos, 0 °C) and purifying crude by flash column chromatography over Florisil® using *n*-pentane/ethyl ether 97:3 as eluent, compound **II-2b** (44.3 mg, 0.104 mmol) was obtained in 52% yield as a colorless oil.

Compound **2b** was obtained with a 99:1 enantiomeric ratio determined by SFC using Chiralpak-ID column [CO_2/MeOH (90:10)], 1.0 mL/min, τ_{major}= 11.6 min, τ_{minor}= 13.0 min. **[α]$^{20}_{D}$**= –29.0 (*c* = 1.0, $CHCl_3$). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.35 – 7.20 (m, 10H), 3.74 (s, 2H), 3.73 (s, 2H), 3.66 – 3.59 (m, 2H), 2.31 – 2.13 (m, 2H), 2.09 – 1.99 (m, 1H), 1.24 (s, 6H), 1.23 (s, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 138.8, 138.6, 129.2, 129.1, 128.5, 128.5, 127.0, 126.9, 83.6, 46.3, 44.0, 36.2, 35.9, 28.7, 24.9, 24.8. [note: the carbon attached to boron was not observed due to quadrupole broadening caused by the ^{11}B nucleus]. **HRMS-ESI$^+$** m/z calculated for $C_{24}H_{31}BO_2S_2Na$ $[M+Na]^+$: 449.1750 found, 449.1764.

(–)-2-[(1*R*,2*S*,3*R*)-2,3-Diphenylcyclobutyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, **II-2c**.

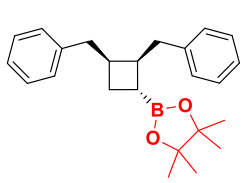


II-2c

From **II-1c** (41.3 mg, 0.2 mmol), following the general procedure described above ((*R*)-DM-Segphos, 0 °C) and purifying crude by flash column chromatography over Florisil® using *n*-pentane/ethyl ether 90:10 as eluent, compound **II-2c** (47 mg, 0.14 mmol) was obtained in 70% yield as white solid.

Compound **II-2c** was obtained with a 97:3 enantiomeric ratio determined by SFC using Chiralpak-IC column [CO_2/MeOH (99:1)], 1.0 mL/min, τ_{major}= 10.7 min, τ_{minor}= 11.6 min. **mp** = 75-77 ºC. **[α]$^{20}_{D}$** = –59.4 (*c* = 1.0, $CHCl_3$). **^{1}H RMN** (300 MHz, $CDCl_3$): δ 7.03 (m, 10H), 4.07 (d, *J* = 5.5 Hz, 2H), 2.64 – 2.44 (m, 2H), 2.44 – 2.27 (m, 1H), 1.31 (s, 12H). **^{13}C RMN** (75 MHz, $CDCl_3$): δ 141.9, 141.7, 128.0, 127.9, 127.6, 125.5, 125.5, 83.3, 46.5, 45.0, 25.9, 24.9, 24.8. [note: the carbon attached to boron was not observed due to quadrupole broadening caused by the ^{11}B nucleus]. **HRMS-EI$^+$** m/z calculated for $C_{22}H_{27}BO_2$ $[M]^+$: 334.2104, found 334.2089.

(–)-2-[(1*R*,2*S*,3*S*)-2,3-Dibenzylcyclobutyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, **II-2d**.



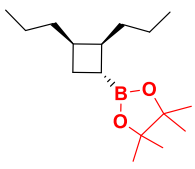
II-2d

From **II-1d** (46.9 mg, 0.2 mmol), following the general procedure described above ((*R*)-DM-Segphos, -20 °C) and purifying crude by flash column chromatography over Florisil® using *n*-pentane/ethyl ether 90:10 as eluent, compound **II-2d** (65.9 mg, 0.18 mmol) was obtained in 91% yield as a colorless oil.

$[\alpha]^{20}_D$= –22.6 (*c* = 1.0, $CHCl_3$). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.33 – 7.25 (m, 4H), 7.24 – 7.14 (m, 6H), 2.99 – 2.67 (m, 6H), 2.05 – 1.91 (m, 1H), 1.86 – 1.70 (m, 2H), 1.12 (s, 6H), 1.10 (s, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 141.5, 141.1, 129.0, 128.8, 128.3, 128.3, 125.7, 125.7, 82.9, 40.5, 39.0, 37.7, 35.9, 25.1, 24.8, 24.7. [note: the carbon attached to boron was not observed due to quadrupole broadening caused by the ^{11}B nucleus]. **HRMS-EI$^+$** m/z calculated for $C_{24}H_{31}BO_2$ $[M]^+$: 362.2417, found 362.2411.

Compound **II-2d** was transformed into **II-23** through oxidation followed by benzoylation to determine the enantiomeric ratio (See compound **II-23**).

(–)-2-[(1*R*,2*S*,3*R*)-2,3-Dipropylcyclobutyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, **II-2e**.



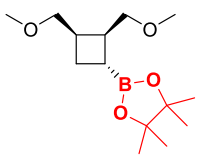
II-2e

From **II-1e** (27.6 mg, 0.2 mmol), following the general procedure described above ((*R*)-DM-Segphos, -20 °C) and purifying crude by flash column chromatography over Florisil® using *n*-pentane/ethyl ether 95:5 as eluent, compound **II-2e** (45.2 mg, 0.17 mmol) was obtained in 85% yield as a colorless oil.

[α]$^{20}_{D}$= –28.0 (*c* = 1.0, $CHCl_3$). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 2.35 – 2.13 (m, 2H), 1.92 (m, 1H), 1.62 – 1.38 (m, 1H), 1.41 – 0.91 (m, 21H), 0.80 (m, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 82.9, 39.5, 37.5, 33.7, 32.3, 26.1, 24.9, 24.8, 20.8, 20.7, 14.6, 14.4. [note: the carbon attached to boron was not observed due to quadrupole broadening caused by the ^{11}B nucleus]. **HRMS-ESI^{+}** m/z calculated for $C_{16}H_{31}BO_2$ $[M]^+$: 266.2417, found 266.2405.

Compound **II-2e** was transformed into **II-24e** through oxidation followed by benzoylation to determine the enantiomeric ratio (See compound **II-24e**).

(–)-2-[(1*R*,2*S*,3*R*)-2,3-bis(Methoxymethyl)cyclobutyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, **II-2f**.



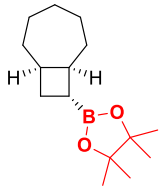
II-2f

From **II-1f** (28.4 mg, 0.2 mmol), following the general procedure described above ((*R*)-DM-Segphos, -20 °C) and purifying crude by flash column chromatography over Florisil® using *n*-pentane/ethyl ether 70:30 as eluent, compound **II-2f** (50.3 mg, 0.19 mmol) was obtained in 93% yield as a yellowish oil.

[α]$^{20}_{D}$= –28.4 (*c* = 1.0, $CHCl_3$). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 3.55 – 3.43 (m, 2H), 3.43 – 3.31 (m, 2H), 3.29 (s, 3H), 3.27 (s, 3H), 2.74 – 2.60 (m, 2H), 2.08 – 1.96 (m, 1H), 1.78 (td, *J* = 10.3, 5.0 Hz, 1H), 1.54 (dt, *J* = 10.3, 6.7 Hz, 1H), 1.21 (s, 12H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 83.2, 73.9, 73.5, 58.9, 58.7, 37.8, 36.1, 24.9, 24.8, 23.9. [note: the carbon attached to boron was not observed due to quadrupole broadening caused by the ^{11}B nucleus]. **HRMS-ESI^{+}** m/z calculated for $C_{14}H_{27}BO_4Na$ $[M+Na]^+$: 293.1894, found 293.1898.

Compound **II-2f** was transformed into **II-24f** through oxidation followed by benzoylation to determine the enantiomeric ratio (See compound **II-24f**).

(–)-2-[(1*R*,7*S*,8*R*)-Bicyclo[5.2.0]nonan-8-yl)]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, **II-2g**.



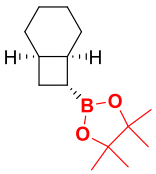
II-2g

From **II-1g** (24.4 mg, 0.2 mmol), following the general procedure described above ((*R*)-DM-Segphos, -20 °C) and purifying crude by flash column chromatography over Florisil® using *n*-pentane/ethyl ether 90:10 as eluent, compound **II-2g** (39.0 mg, 0.156 mmol) was obtained in 78% yield as a yellowish oil.

$[\alpha]^{20}_D$= –25.0 (*c* = 1.0, $CHCl_3$). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 2.51 – 2.36 (m, 2H), 2.12 – 1.98 (m, 1H), 1.84 – 1.71 (m, 3H), 1.71 – 1.35 (m, 7H), 1.25 (s, 6H), 1.25 (s, 6H), 1.12 – 1.01 (m, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 82.9, 40.6, 38.7, 34.6, 33.3, 32.6, 29.8, 29.5, 25.7, 24.9, 24.8. [note: the carbon attached to boron was not observed due to quadrupole broadening caused by the ^{11}B nucleus]. **HRMS-EI$^+$** m/z calculated for $C_{15}H_{29}BO_2$ $[M]^+$: 250.2104, found 250.2113.

Compound **II-2g** was transformed into **II-24g** through oxidation followed by benzoylation to determine the enantiomeric ratio (See compound **II-24g**).

(–)-2-[(1*R*,6*S*,7*R*)-Bicyclo[4.2.0]octan-7-yl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, **II-2h**.



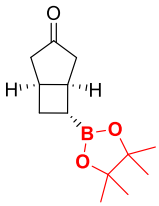
II-2h

From **II-1h** (21.6 mg, 0.2 mmol), following the general procedure described above ((*R*)-DM-Segphos, -20 °C) and purifying crude by flash column chromatography over Florisil® using *n*-pentane/ethyl ether 95:5 as eluent, compound **II-2h** (44.9 mg, 0.19 mmol) was obtained in 95% yield as a yellowish oil.

[α]$^{20}_{D}$= –25.2 (*c* = 1.0, $CHCl_3$). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 2.42 – 2.22 (m, 2H), 1.98 – 1.85 (m, 1H), 1.74 – 1.66 (m, 2H), 1.65 – 1.51 (m, 2H), 1.52 – 1.29 (m, 6H), 1.24 (s, 12H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 82.9, 35.4, 33.4, 28.8, 28.4, 26.8, 24.9, 24.9, 23.2, 22.7. [note: the carbon attached to boron was not observed due to quadrupole broadening caused by the ^{11}B nucleus]. **HRMS-EI^{+}** m/z calculated for $C_{14}H_{25}BO_2$ $[M]^{+}$: 236.1948, found 236.1947.

Compound **II-2h** was transformed into **II-24h** through oxidation followed by benzoylation to determine the enantiomeric ratio (See compound **II-24h**).

(–)-(1*S*,5*S*,6*R*)-6-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)bicyclo[3.2.0]heptan-3-one, **II-2i**.



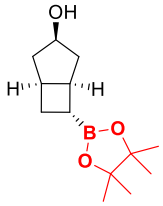
II-2i

From **II-1i** (21.6 mg, 0.2 mmol), following the general procedure described above ((*R*)-DM-Segphos, 0 °C) and purifying crude by flash column chromatography over Florisil® using *n*-pentane/ethyl ether 90:10 as eluent, compound **II-2i** (43.0 mg, 0.18 mmol) was obtained in 91% yield as a yellowish oil.

[α]$^{20}_{D}$= –24.0 (*c* = 1.0, $CHCl_3$). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 3.07 – 2.92 (m, 2H), 2.57 – 2.40 (m, 2H), 2.38 – 2.25 (m, 1H), 2.19 (d, *J* = 19.2 Hz, 2H), 1.84 – 1.72 (m, 1H), 1.63 – 1.51 (m, 1H), 1.25 (s, 12H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 221.5, 83.2, 45.9, 45.0, 35.9, 34.1, 27.7, 24.7. [note: the carbon attached to boron was not observed due to quadrupole broadening caused by the ^{11}B nucleus]. **HRMS-EI^{+}** m/z calculated for $C_{13}H_{21}BO_3$ $[M]^{+}$: 236.1584, found 236.1577.

Compound **II-2i** was transformed into **II-24i** through oxidation followed by benzoylation to determine the enantiomeric ratio (See compound **II-24i**).

(–)-(1*S*,3*R*,5*S*,6*R*)-6-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)bicyclo[3.2.0]heptan-3-ol, **II-2j**.



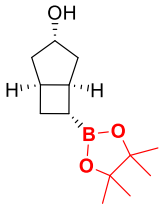
II-2j

From **II-1j** (22.0 mg, 0.2 mmol), following the general procedure described above ((*R*)-DM-Segphos, -20 °C) and purifying crude by flash column chromatography over Florisil® using *n*-pentane/ethyl ether 80:20 as eluent, compound **II-2j** (34.8 mg, 0.15 mmol) was obtained in 73% yield as a yellowish oil.

[α]$^{20}_{D}$= –33.0 (*c* = 1.0, $CHCl_3$). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 4.52 – 4.38 (m, 1H), 2.75 (m, 2H), 2.29 – 2.14 (m, 1H), 2.04 – 1.89 (m, 3H), 1.89 – 1.79 (m, 1H), 1.75 (d, *J* = 12.5 Hz, 2H), 1.52 (s, 1H), 1.26 (s, 12H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 83.0, 77.9, 44.3, 43.4, 39.3, 37.6, 27.1, 24.9. [note: the carbon attached to boron was not observed due to quadrupole broadening caused by the ^{11}B nucleus]. **HRMS-ESI^{+}** m/z calculated for $C_{13}H_{23}BO_3Na$ $[M+Na]^{+}$: 261.1632, found 261.1637.

Compound **II-2j** was transformed into **II-25j** through benzoylation followed by oxidation to determine the enantiomeric ratio (See compound **II-25j**).

(–)-(1*S*,3*S*,5*S*,6*R*)-6-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)bicyclo[3.2.0]heptan-3-ol, **II-2k**.



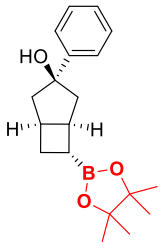
II-2k

From **II-1k** (22.0 mg, 0.2 mmol), following the general procedure described above ((*R*)-DM-Segphos, -20 °C) and purifying crude by flash column chromatography over Florisil® using *n*-pentane/ethyl ether 80:20 as eluent, compound **II-2k** (36.2 mg, 0.15 mmol) was obtained in 76% yield as a colorless oil.

$[\alpha]^{20}_D$= –32.3 (*c* = 1.0, $CHCl_3$). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 4.85 – 4.70 (m, 1H), 2.85 – 2.72 (m, 2H), 2.23 – 2.11 (m, 1H), 1.95 – 1.84 (m, 2H), 1.72 – 1.49 (m, 5H), 1.24 (s, 12H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 83.2, 74.2, 43.2, 42.5, 37.9, 36.0, 26.4, 25.0, 24.9. [note: the carbon attached to boron was not observed due to quadrupole broadening caused by the ^{11}B nucleus]. **HRMS-ESI$^+$** m/z calculated for $C_{13}H_{23}BO_3Na$ $[M+Na]^+$: 261.1632, found 261.1637.

Compound **II-2k** was transformed into **II-25k** through benzoylation followed by oxidation to determine the enantiomeric ratio (See compound **II-25k**).

(–)-(1*S*,3*R*,5*S*,6*R*)-3-Phenyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)bicyclo[3.2.0]heptan-3-ol, **II-2l**.



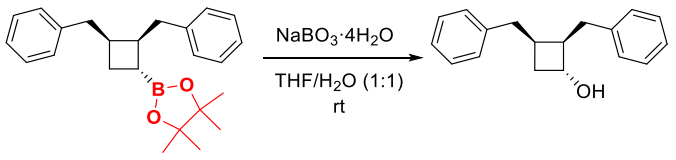
II-2l

From **II-1l** (37.26 mg, 0.2 mmol), following the general procedure described above ((*R*)-DTBM-Segphos, 0 °C) and purifying crude by flash column chromatography over Florisil® using *n*-pentane/ethyl ether 80:20 as eluent, compound **II-2l** (57.2 mg, 0.18 mmol) was obtained in 91% yield as a yellowish solid.

Compound **II-2l** was obtained with a 98:2 enantiomeric ratio determined by SFC using Chiralpak-ID column [CO_2/MeOH (95:5)], 3.0 mL/min, τ_{major}= 5.1 min, τ_{minor}= 6.4 min. **mp** = 87-89 ºC. **[α]$^{20}_D$**= –35.2 (*c* = 1.0, $CHCl_3$). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.48 (d, *J* = 7.2 Hz, 2H), 7.34 (t, *J* = 7.5 Hz, 2H), 7.22 (t, *J* = 7.2 Hz, 1H), 3.05 – 2.93 (m, 2H), 2.35 – 2.16 (m, 4H), 2.17 – 2.01 (m, 3H), 1.80 (s, 1H), 1.28 (s, 12H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 148.0, 128.2, 126.7, 125.0, 87.0, 82.9, 49.8, 49.3, 40.0, 38.3, 26.5, 24.8. [note: the carbon attached to boron was not observed due to quadrupole broadening caused by the ^{11}B nucleus]. **HRMS-ESI$^+$** m/z calculated for $C_{19}H_{27}BO_3Na$ $[M+Na]^+$: 337.1945, found 337.1961.

2.6.5. Derivatizations to determine the enantiomeric excess of cyclobutylboronates **II-2d**, **II-2e**, **II-2f, II-2g**, **II-2h**, **II-2i**, **II-2j**, **II-2k**.

*2.6.5.1. Synthesis of (–)-(1R,2R,3R)-2,3-dibenzylcyclobutan-1-ol, **II-23**.*

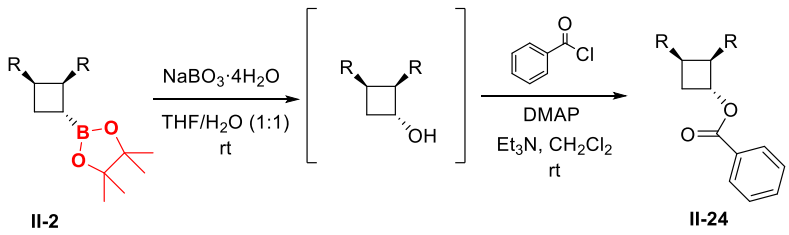


II-2d **II-23**

$NaBO_3 \cdot 4H_2O$ (4 equiv) was added to a solution of **II-2d** (65 mg, 0,174 mmol, 1 equiv) in THF/H_2O (1:1, 10.8 mL/mmol cyclobutylboronate). The reaction mixture was stirred overnight at room temperature and then quenched with H_2O and extracted with Et_2O (x3). The combined organic phases were washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuum to afford the alcohol. The residue was purified by flash column chromatography on silica gel using hexanes/ether 80:20 as eluent. Compound **II-23** (41 mg, 0.162 mmol) was obtained in 93% global yield as a yellow oil.

$[\alpha]^{20}_D$= –78.8 (*c* = 1.0, $CHCl_3$). Compound **II-23** was obtained with a 96:4 enantiomeric ratio determined by SFC using Chiralpak-IB column [CO_2/MeOH (80:20)], 2.0 mL/min, τ_{major}= 3.9 min, τ_{minor}= 4.4 min.**^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.37 – 7.13 (m, 10H), 4.24 (q, *J* = 7.5 Hz, 1H), 2.97 (d, *J* = 9.5 Hz, 1H), 2.88 (d, *J* = 7.5 Hz, 2H), 2.70 – 2.53 (m, 3H), 2.11 (dd, *J* = 11.6, 7.5 Hz, 1H), 1.90 – 1.77 (m, 1H), 1.58 (br, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 141.1, 140.8, 128.8, 128.7, 128.6, 128.5, 126.1, 126.0, 71.5, 49.5, 36.6, 35.1, 34.1, 31.0. **HRMS-ESI$^+$** m/z calculated for $C_{18}H_{20}ONa$ $[M+Na]^+$: 275.1406, found 275.1413.

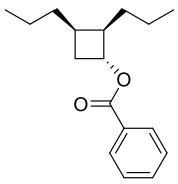
*2.6.5.2. Procedure for synthesis of benzoates **II-24**.*



$NaBO_3 \cdot 4H_2O$ (4 equiv) was added to a solution of the corresponding cyclobutylboronate **II-2** (1 equiv) in THF/H_2O (1:1, 10.8 mL/mmol cyclobutylboronate). The reaction mixture was stirred overnight at room temperature and then quenched with H_2O and extracted with Et_2O (x3). The combined organic phases were washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuum to afford the alcohol. This compound was used in the next step without further purification.

To a solution of corresponding alcohol in CH_2Cl_2, 4-dimethylaminopyridine (DMAP) (2.1 equiv), triethylamine (3 equiv) and the corresponding benzyl chloride (2.0 equiv) were added. The reaction mixture was stirred for 30 min at room temperature and then quenched with H_2O. The aqueous layer was extracted with Et_2O (x3) and the combined organic phases were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel.

(–)-(1*R*,2*R*,3*R*)-2,3-Dipropylcyclobutyl benzoate, **II-24e**.

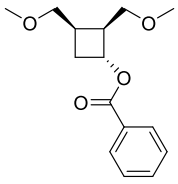


II-24e

From **II-2e** (50 mg, 0.188 mmol), following the general procedure described above, purifying crude by flash column chromatography over silica gel using *n*-pentane/ethyl ether 90:10 as eluent, compound **II-24e** (42 mg, 0.161 mmol) was obtained in 86% global yield as a colorless oil.

Compound **II-24e** was obtained with a 97:3 enantiomeric ratio determined by UHPLC using Chiralpak-IC-3 [Hexane/2-propanol (99.6:0.4)], 1.0 mL/min, τ_{major}= 3.5 min, τ_{minor}= 4.0 min. $[\alpha]^{20}_{D}$= –75.6 (*c* = 1.0, CHCl3). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.04 (d, *J* = 7.5 Hz, 2H), 7.55 (t, *J* = 7.5 Hz, 1H), 7.43 (t, *J* = 7.5 Hz, 2H), 5.02 (q, *J* = 7.5 Hz, 1H), 2.66 – 2.51 (m, 1H), 2.30 – 2.12 (m, 2H), 2.12 – 2.01 (m, 1H), 1.61 – 1.39 (m, 4H), 1.34 – 1.25 (m, 4H), 0.94 (t, *J* = 7.0 Hz, 3H), 0.90 (t, *J* = 7.3 Hz, 3H).**^{13}C NMR** (75 MHz, $CDCl_3$) δ 166.3, 132.9, 130.8, 129.7, 128.4, 74.3, 44.9, 32.7, 32.6, 30.8, 30.4, 21.2, 21.0, 14.4, 14.3. **HRMS-EI^{+}** m/z calculated for $C_{17}H_{24}O_2Na$ $[M]^{+}$: 283.1668 found 283.1680.

(–)-(1*R*,2*S*,3*R*)-2,3-Bis(methoxymethyl)cyclobutyl benzoate, **II-24f**.



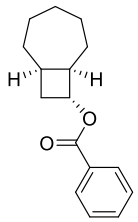
II-24f

From **II-2f** (50 mg, 0.18 mmol), following the general procedure described above, purifying crude by flash column chromatography over silica gel using *n*-pentane/ethyl ether 65:35 as eluent, compound **II-24f** (37 mg, 0.14 mmol) was obtained in 78% global yield as a yellow oil.

$[\alpha]^{20}_{D}$= –67.1 (*c* = 1.0, $CHCl_3$). Compound **II-24f** was obtained with a 97:3 enantiomeric ratio determined by SFC using Chiralpak-ID column [CO_2/MeOH (95:5)], 1.0 mL/min, τ_{major}= 10.5 min, τ_{minor}= 10.0 min. **^{1}H**

NMR (300 MHz, $CDCl_3$) δ 8.04 (d, *J* = 7.4 Hz, 2H), 7.55 (t, *J* = 7.4 Hz, 1H), 7.43 (t, *J* = 7.4 Hz, 2H), 5.18 (q, *J* = 7.6 Hz, 1H), 3.62 – 3.46 (m, 4H), 3.37 (s, 3H), 3.34 (s, 3H), 2.96 – 2.84 (m, 1H), 2.69 – 2.55 (m, 1H), 2.40 – 2.17 (m, 2H).**^{13}C NMR** (75 MHz, $CDCl_3$) δ 166.3, 133.0, 130.4, 129.7, 128.4, 73.0, 71.3, 70.6, 59.0, 58.9, 44.5, 30.4, 30.1. **HRMS-ESI$^+$** m/z calculated for $C_{15}H_{20}O_4Na$ $[M+Na]^+$: 287.1253, found 287.1255.

(–)-(1*R*,7*R*,8*R*)-Bicyclo[5.2.0]nonan-8-yl benzoate, **II-24g**.

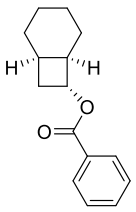


II-24g

From **II-2g** (39 mg, 0.156 mmol), following the general procedure described above, purifying crude by flash column chromatography over silica gel using *n*-pentane/ethyl ether 90:10 as eluent, compound **II-24g** (34 mg, 0.14 mmol) was obtained in 90% global yield as a yellowish oil.

$[\alpha]^{20}_D$= –51.4 (*c* = 1.0, $CHCl_3$). Compound **II-24g** was obtained with a 97:3 enantiomeric ratio determined by SFC using Chiralpak-IC column [CO_2/MeOH (99:1)], 1.0 mL/min, τ_{major}= 20.0 min, τ_{minor}= 22.8 min. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.04 (d, *J* = 7.5 Hz, 2H), 7.55 (t, *J* = 7.5 Hz, 1H), 7.43 (t, *J* = 7.5 Hz, 2H), 5.02 (q, *J* = 7.5 Hz, 1H), 2.66 – 2.51 (m, 1H), 2.30 – 2.12 (m, 2H), 2.12 – 2.01 (m, 1H), 1.61 – 1.39 (m, 4H), 1.34 – 1.25 (m, 4H), 0.94 (t, *J* = 7.0 Hz, 3H), 0.90 (t, *J* = 7.3 Hz, 3H).**^{13}C NMR** (75 MHz, $CDCl_3$) δ 166.5, 132.9, 130.7, 129.7, 128.4, 74.9, 46.0, 33.3, 33.1, 32.5, 32.1, 31.4, 30.5, 28.3. **HRMS-EI$^+$** m/z calculated for $C_{16}H_{20}O_2$ $[M]^+$: 244.1463, found 244.1469.

(–)-(1*R*,6*R*,7*R*)-Bicyclo[4.2.0]octan-7-yl benzoate, **II-24h**.

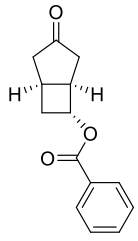


II-24h

From **II-2h** (57 mg, 0.24 mmol), following the general procedure described above, purifying crude by flash column chromatography over silica gel using *n*-pentane/ethyl ether 90:10 as eluent, compound **II-24h** (50.6 mg, 0.22 mmol) was obtained in 96% global yield as a yellowish oil.

[α]$^{20}_{D}$= –39.5 (*c* = 1.0, $CHCl_3$). Compound **II-24h** was obtained with a 96:4 enantiomeric ratio determined by SFC using Chiralpak-IC column [CO_2/MeOH (99:1)], 1.0 mL/min, τ_{major}= 17.7 min, τ_{minor}= 19.6 min. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.04 (d, *J* = 7.4 Hz, 2H), 7.55 (t, *J* = 7.4 Hz, 1H), 7.43 (t, *J* = 7.4 Hz, 2H), 5.31 (q, *J* = 7.5 Hz, 1H), 2.60 – 2.49 (m, 1H), 2.26 – 2.14 (m, 1H), 2.15 – 2.06 (m, 2H), 2.04 – 1.92 (m, 1H), 1.86 – 1.77 (m, 1H), 1.70 – 1.58 (m, 2H), 1.48 – 1.39 (m, 2H), 1.34 – 1.22 (m, 1H), 1.17 – 1.01 (m, 1H).**^{13}C NMR** (75 MHz, $CDCl_3$) δ 166.4, 132.8, 130.6, 129.6, 128.3, 70.7, 40.7, 34.4, 30.0, 25.2, 24.8, 23.7, 22.5. **HRMS-EI$^+$** m/z calculated for $C_{15}H_{18}O_2$ $[M]^+$: 230.1307, found 230.1304.

(–)-(1*S*,5*R*,6*R*)-3-Oxobicyclo[3.2.0]heptan-6-yl benzoate, **II-24i**.



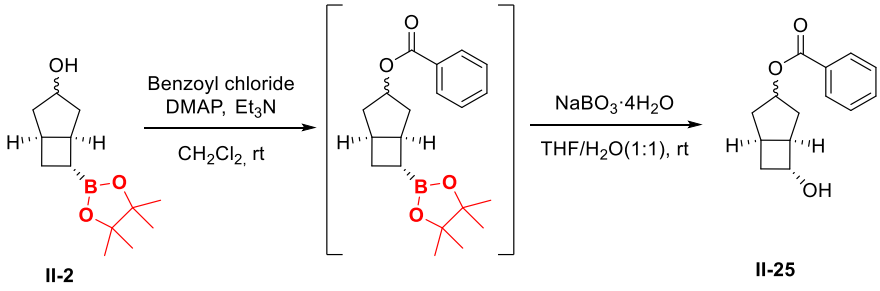
II-24i

From **II-2i** (43 mg, 0.18 mmol), following the general procedure described above, purifying crude by flash column chromatography over silica gel using *n*-pentane/ethyl ether 90:10 as eluent, compound **II-24i** (30 mg, 0.13 mmol) was obtained in 72% global yield as a yellowish oil.

[α]$^{20}_{D}$= –7.9 (*c* = 1.0, $CHCl_3$). Compound **II-24i** was obtained with a 96:4 enantiomeric ratio determined by SFC using Chiralpak-IC column [CO_2/MeOH (90:10)], 1.0 mL/min, τ_{major}= 18.4 min,

τ_{minor}= 15.6 min. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.04 (d, *J* = 7.3 Hz, 2H), 7.56 (t, *J* = 7.3 Hz, 1H), 7.45 (t, *J* = 7.3 Hz, 2H), 4.96 (q, *J* = 7.1 Hz, 1H), 3.26 – 3.13 (m, 1H), 3.12 – 2.97 (m, 1H), 2.70 – 2.46 (m, 4H), 2.37 – 2.20 (m, 2H).**^{13}C NMR** (75 MHz, $CDCl_3$) δ 218.0, 166.1, 133.3, 130.0, 129.7, 128.5, 74.6, 44.3, 43.7, 43.1, 34.2, 28.3. **HRMS-EI^{+}** m/z calculated for $C_{14}H_{14}O_3$ $[M]^{+}$: 230.0943, found 230.0941.

*2.6.5.3. Procedure for synthesis of benzoates **II-25**.*

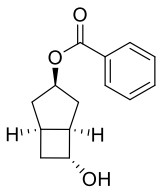


To a solution of alcohol in CH_2Cl_2, 4-dimethylaminopyridine (DMAP) (2.1 equiv), triethylamine (3 equiv) and the benzyl chloride (2.0 equiv) were added. The reaction mixture was stirred for 30 min at room temperature and then quenched with H_2O. The aqueous layer was extracted with Et_2O (x3) and the combined organic phases were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on Florisil® using *n*-pentane/ethyl ether 90:10 as eluent.

$NaBO_3{\cdot}4H_2O$ (4 equiv) was added to a solution of cyclobutylboronate (1 equiv) in THF/H_2O (1:1, 10.8 mL/mmol cyclobutylboronate). The reaction mixture was stirred overnight at room temperature and then quenched with H_2O and extracted with Et_2O (x3). The combined organic phases were washed with brine, dried over Na_2SO_4, filtered and

concentrated in vacuum to afford the alcohol. The residue was purified by flash column chromatography on silica gel using hexanes/ethyl acetate 70:30 as eluent.

(–)-(1*S*,3*R*,5*R*,6*R*)-6-Hydroxybicyclo[3.2.0]heptan-3-yl benzoate, **II-25j**.

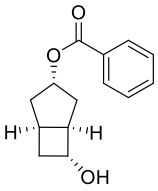


II-25j

From **II-2j** (30 mg, 0.125 mmol), following the general procedure described above, compound **II-25j** (15 mg, 0.065 mmol) was obtained in 52% overall yield as a yellow oil.

[α]$^{20}_{D}$= –18.7 (*c* = 1.0, $CHCl_3$). Compound **II-25j** was obtained with a 97:3 enantiomeric ratio determined by SFC using Chiralpak-IC column [CO_2/MeOH (95:5)], 3.0 mL/min, τ_{major}= 6.0 min, τ_{minor}= 6.9 min. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.02 (d, *J* = 7.3 Hz, 2H), 7.56 (t, *J* = 7.3 Hz, 1H), 7.44 (t, *J* = 7.3 Hz, 2H), 5.62 (t, *J* = 5.1 Hz, 1H), 4.42 – 4.29 (m, 1H), 2.96 – 2.82 (m, 1H), 2.81 – 2.70 (m, 1H), 2.42 – 2.28 (m, 1H), 2.21 – 1.92 (m, 5H), 1.88 (br, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 166.3, 133.1, 130.8, 129.6, 128.6, 80.7, 72.6, 49.9, 39.4, 38.4, 36.4, 31.8. **HRMS-ESI$^+$** m/z calculated for $C_{14}H_{16}O_3Na$ $[M+Na]^+$: 255.0991, found 255.0994.

(–)-(1*S*,3*S*,5*R*,6*R*)-6-Hydroxybicyclo[3.2.0]heptan-3-yl benzoate, **II-25k**.



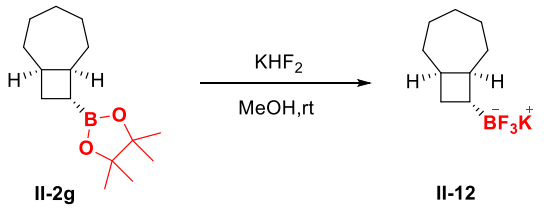
II-25k

From **II-2k** (39 mg, 0.164 mmol), following the general procedure described above, compound **II-25k** (30.4 mg, 0.131 mmol) was obtained in 78% global yield as a yellow oil.

[α]$^{20}_{D}$= –12.0 (*c* = 1.0, $CHCl_3$). Compound **II-25k** was obtained with a 97:3 enantiomeric ratio determined by SFC using

Chiralpak-ID column [CO_2/MeOH (95:5)], 3.0 mL/min, τ_{major}= 11.1 min, τ_{minor}= 10.0 min.**^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.02 (d, *J* = 7.5 Hz, 2H), 7.55 (t, *J* = 7.5 Hz, 1H), 7.43 (t, *J* = 7.5 Hz, 2H), 5.62 – 5.47 (m, 1H), 4.15 – 4.01 (m, 1H), 2.93 – 2.81 (m, 1H), 2.81 – 2.69 (m, 1H), 2.21 (m, 1H), 2.11 (m, 2H), 2.08 – 2.00 (m, 1H), 1.94 – 1.79 (m, 2H), 1.71 (br, 1H).**^{13}C NMR** (75 MHz, $CDCl_3$) δ 166.6, 133.0, 130.6, 129.7, 128.5, 77.2, 72.4, 47.7, 37.7, 36.8, 36.0, 29.5. **HRMS-ESI$^+$** m/z calculated for $C_{14}H_{16}O_3Na$ $[M+Na]^+$: 255.0991, found 255.0991.

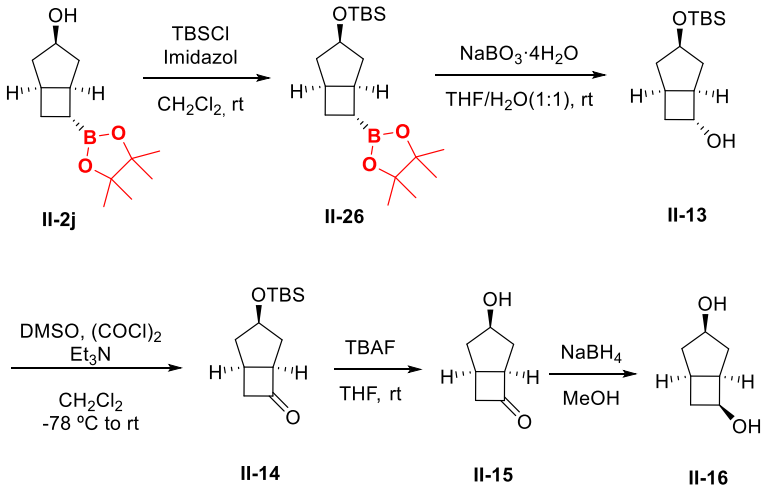
2.6.6. Procedure for the synthesis of potassium (+)-((1*R*,7*S*,8*R*)-bicyclo[5.2.0]nonan-8-yl)trifluoroborate, **II-12**.



To a solution of **II-2g** (175 mg, 0.700 mmol, 1.00 equiv) in MeOH (3 mL) in a 20 mL vial containing a stir bar. An aqueous solution of KHF_2 (4.5M, 4.5 equiv) was added to the vial. The solution was stirred at room temperature for 6 h. After the evaporation of the solvent under vacuum, the residual pinacol was removed by adding three portions of Et_2O, retiring the resulting solution. The solid obtained was triturated with acetone (x7) and filtered through a plug of Celite®. The acetone solution was evaporated to yield compound **II-12** (129 mg, 0.56 mmol) in 80% yield as white solid.

[α]$^{20}_{D}$= +46.8 (*c* = 1.0, $(CH_3)_2CO$). **^{1}H NMR** (300 MHz, Acetone) δ 2.42 – 2.19 (m, 2H), 1.97 – 1.84 (m, 1H), 1.84 – 1.69 (m, 3H), 1.67 – 1.49 (m, 3H), 1.48 – 1.15 (m, 3H), 1.14 – 0.98 (m, 2H), 0.95 – 0.75 (m, 1H). **^{13}C NMR** (75 MHz, Acetone) δ 41.3, 41.2, 38.8, 35.9, 34.8, 33.5, 30.8, 26. 9, 26.9. **HRMS-ESI^{-}** m/z calculated for $C_9H_{15}BF_3$ [M-K]$^{-}$: 191.1224, found 191.1238.

2.6.7. Synthesis of (–)-(1*R*,3*R*,5*R*,6*S*)-Bicyclo[3.2.0]heptane-3,6-diol, **II-16**. [122]

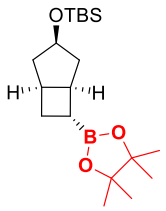


(–)-tert-Butyldimethyl[((1*S*,3*R*,5*S*,6*R*)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl]bicyclo[3.2.0]heptan-3-yl)oxy)silane, **II-26**.

To a solution of **II-2j** (104 mg, 0.44 mmol, 1 equiv) and imidazole (39 mg, 0.57 mmol, 1.2 equiv) in CH_2Cl_2 (2 mL) was added TBSCl (76.9, 0.51 mmol, 1.1 equiv) at room temperature. The reaction mixture was stirred at

[122] Derrien, N; Dousson, C. B.; Roberts, S. M.; Berens, U.; Burk M. J.; Ohff, M. *Tetrahedron: Asymmetry*, **1999**, *10*, 3341.

room temperature until full conversion is observed by TLC (4 h). Et_2O and water were added, and the layers were separated. The combined organic phases were washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuum. Solvent was removed under reduced pressure and crude was purified by flash column chromatography over Florisil® using *hexanes*/ethyl ether 95:5 as eluent. Compound **II-26** (132 mg, 0.375 mmol) was obtained in 87% yield as colorless oil.

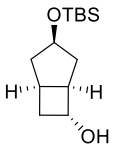


II-26

$[\alpha]^{20}_D$= –28.2 (*c* = 1.0, $CHCl_3$). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 4.45 – 4.34 (m, 1H), 2.80 – 2.63 (m, 2H), 2.17 – 2.02 (m, 2H), 1.89 – 1.79 (m, 2H), 1.80 – 1.64 (m, 3H), 1.26 (s, 12H), 0.89 (s, 9H), 0.06 (s, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 82.9, 77.8, 44.1, 43.4, 39.3, 37.5, 26.7, 26.1, 24.9, 24.9, 18.2, -4.7. **HRMS-ESI$^+$** m/z calculated for $C_{19}H_{37}BO_3SiNa$ $[M+Na]^+$: 375.2497, found 375.2482.

(–)-(1*S*,3*R*,5*R*,6*R*)-3-((tert-butyldimethylsilyl)oxy)bicyclo [3.2.0]heptan-6-ol, **II-13**.

$NaBO_3 \cdot 4H_2O$ (231 mg, 1.5 mmol, 4 equiv) was added to a solution of cyclobutylboronate **II-26** (132 mg, 0.375 mmol, 1 equiv) in THF/H_2O (1:1, 4.5 mL). The reaction mixture was stirred overnight at room temperature and then quenched with H_2O and extracted with Et_2O (x3). The combined organic phases were washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuum to afford the alcohol. The residue was purified by flash column chromatography on silica gel using *hexanes*/ethyl acetate 4:1 as eluent. Compound **II-13** (90.5 mg, 0.375 mmol) was obtained in quantitative yield as colorless oil.

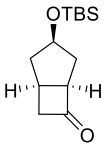


II-13

[α]$^{20}_{D}$= –14.7 (*c* = 1.0, $CHCl_3$). **^{1}H NMR** (300 MHz, $CDCl_3$) 4.43 – 4.32 (m, 2H), 2.80 – 2.67 (m, 1H), 2.67 – 2.55 (m, 1H), 2.41 – 2.25 (m, 1H), 2.07 – 1.90 (m, 1H), 1.84 – 1.73 (m, 3H), 1.68 – 1.56 (m, 2H), 0.89 (s, 9H), 0.06 (s, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 77.3, 73.0, 50.0, 42.3, 41.2, 36.5, 31.7, 26.0, 18.1, -4.7, -4.8. **HRMS-ESI^{+}** m/z calculated for $C_{13}H_{26}O_2SiNa$ $[M+Na]^{+}$: 265.1594, found 265.1587.

(–)-(1*R*,3*R*,5*R*)-3-((*tert*-Butyldimethylsilyl)oxy)bicyclo[3.2.0]heptan-6-one, **II-14**.

DMSO (55 mg, 0.7 mmol, 2 equiv) and $(COCl)_2$ (53 mg, 0.42 mmol, 1,2 equiv) were added to a stirred flask with CH_2Cl_2 (2 mL) at -78 ºC and the mixture was stirred at -78 ºC for 30 minutes. Alcohol **II-13** (86 mg, 0,35 mmol, 1 equiv) dissolved in CH_2Cl_2 (2 mL) was added slowly to the mixture and it was stirred for 1 hour at -78 ºC. Et_3N (142 mg, 1.4 mmol, 4 equiv) was added at -78 ºC and the reaction was stirred at room temperature until full conversion is observed by TLC (2h). The reaction was quenched with H_2O and extracted with Et_2O (x3). The combined organic phases were washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuum to afford the alcohol. The residue was purified by flash column chromatography on silica gel using *hexanes*/Ethyl acetate 90:10 as eluent. Compound **II-14** (74 mg, 0.306 mmol) was obtained in 87% yield as colorless oil.



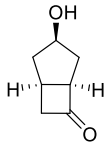
II-14

[α]$^{20}_{D}$= –71.6 (*c* = 1.0, $CHCl_3$). **^{1}H NMR** (300 MHz, $CDCl_3$) 4.44 (br, 1H), 3.63 – 3.51 (m, 1H), 3.23 – 2.98 (m, 2H), 2.94 – 2.80 (m, 1H), 2.15 (d, *J* = 13.6 Hz, 1H), 1.95 – 1.88 (m, 2H), 1.86 – 1.73 (m, 1H), 0.84 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 213.6, 76.0, 63.6, 53.3, 41.4, 41.3, 28.7, 25.7,

17.9, -4.9. **HRMS-EI**$^{+}$ m/z calculated for $C_{13}H_{24}O_2Si$ $[M]^{+}$: 240.1546, found 240.1553.

(–)-(1*R*,3*R*,5*R*)-3-Hydroxybicyclo[3.2.0]heptan-6-one, **II-15**.

TBAF (65.3 mg, 0.250 mmol, 1,2 equiv) was added slowly to a solution of **II-14** (50 mg, 0.208 mmol, 1 equiv) in THF (1 mL). The reaction is stirred at room temperature until full conversion is observed by TLC (4 h). The reaction was quenched with H_2O and extracted with Et_2O (x3). The combined organic phases were washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuum to afford the alcohol. The residue was purified by flash column chromatography on silica gel using *hexanes*/Ethyl acetate 80:20 as eluent. Compound **II-15** (61 mg, 0.254 mmol) was obtained in 80% yield as colorless oil.

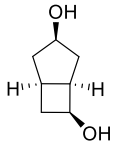


II-15

The spectral data for **II-15** matched those previously reported.[122] **^{1}H NMR** ($CDCl_3$, 300 MHz) 4.54 (br, 1H), 3.67 – 3.54 (m, 1H), 3.20 (ddd, *J* = 18.0, 9.6, 3.7 Hz, 1H), 3.08 – 2.97 (m, 1H), 2.96 – 2.85 (m, 1H), 2.19 (d, *J* = 14.2 Hz, 1H), 2.02 – 1.93 (m, 2H), 1.92 – 1.84 (m, 1H), 1.82 (s, 1H). **$[\alpha]^{20}_D$**= –108.0 (*c* = 1.0, $CHCl_3$).

(–)-(1*R*,3*R*,5*R*,6*S*)-Bicyclo[3.2.0]heptane-3,6-diol, **II-16**.

Compound **II-16** was synthetized following a previously reported procedure.[122]



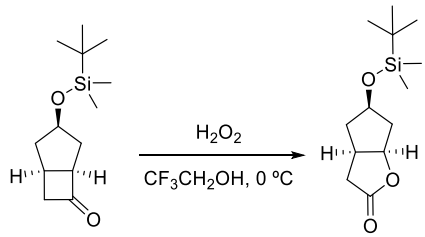
II-16

To a MeOH (0.5 mL) solution containing $NaBH_4$ (8 mg, 0.2 mmol, 1.3 equiv.) at -78 ºC was added a MeOH (0.1 mL) solution of **II-15** (19 mg, 0.15 mmol, 1 equiv.) dropwise over 0.5 h. The mixture was allowed to stir at this temperature for 3

h, after which time TLC analysis indicated the complete disappearance of the starting material and the appearance of a new product. The reaction was quenched with water (0.3 mL), followed by dilute hydrochloric acid (1 M, 1 mL/mmol of ketone). The aqueous mixture was extracted with ether (x3), which were combined, washed with saturated aqueous NaCl, dried ($MgSO_4$) and concentrated in vacuum to yield a pale yellow oil. The residue was purified by flash column chromatography on silica gel using hexanes/Ethyl acetate 1:1 as eluent. Compound **II-16** (14 mg, 0.109 mmol) was obtained in 73% yield as colorless oil.

The spectral data for **II-16** matched those previously reported.[122] **^{1}H NMR** (300 MHz, C_6D_6) δ 4.53 (br, 1H), 4.26 (br, 1H), 4.17 (t, *J* = 4.5 Hz, 1H), 3.36 (br, 1H), 2.98 (q, *J* = 8.0 Hz, 1H), 2.66 (dtd, *J* = 13.2, 9.0, 1.2 Hz, 1H), 2.28 – 2.19 (m, 1H), 2.15 (d, *J* = 15.1 Hz, 1H), 1.87 (dt, *J* = 13.3, 4.7 Hz, 1H), 1.54 – 1.38 (m, 3H). **$[\alpha]^{20}_D$**= –34.90 (*c* = 1.0, $CHCl_3$).

2.6.8. Procedure for the Baeyer-Villiger Oxidation. Synthesis of (3*aR*,5*R*,6*aR*)-5-((*tert*-butyldimethylsilyl)oxy)hexahydro-2H-cyclopenta[b]furan-2-one, **II-17**.



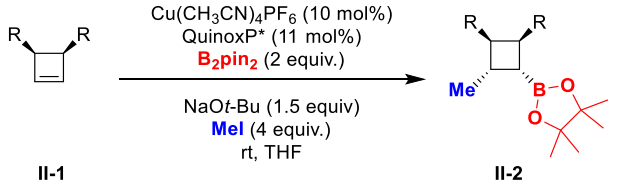
II-14 **II-17**

Compound **II-17** was synthetized following a previously reported procedure.[123] Aqueous 35% hydrogen peroxide (40 mg, 4 equiv) was added at 0 ºC to a 0.4 M solution of cyclobutanone **II-14** (20 mg, 0.083 mmol) in trifluoroethanol (0.3 mL). The resulting reaction mixture was then stirred at 0 ºC until complete conversion of the starting material (96 h). The solvent was removed under vacuum and the residue was dissolved in ether and extracted with 1 M aqueous $Na_2S_2O_3$. The organic layer was dried over $MgSO_4$, concentrated in vacuo and purified by flash column chromatography on silica gel using *n*-hexane/ethyl acetate 4:1 as eluent.

Compound **II-17** (16.8 mg, 0.066 mmol) was obtained in 80% yield as yellow oil (9:1 r.r.). Only the major regioisomer was characterized. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 5.05 (t, *J* = 7.0 Hz, 1H), 4.41 – 4.34 (m, 1H), 3.06 – 2.97 (m, 1H), 2.79 (dd, *J* = 18.1, 11.4 Hz, 1H), 2.52 (dd, *J* = 18.1, 3.9 Hz, 1H), 2.14 (d, *J* = 14.9 Hz, 1H), 1.95 – 1.80 (m, 2H), 1.79 – 1.72 (m, 1H), 0.86 (s, 9H), 0.05 (s, 3H), 0.05 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 177.7, 85.3, 74.2, 43.0, 42.6, 37.2, 37.0, 25.8, 18.1, -4.8, -5.0. **HRMS-ESI$^+$** m/z calculated for $C_{13}H_{24}O_3SiNa$ $[M+Na]^+$: 279.1386, found 279.1378.

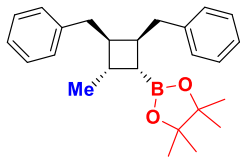
[123] Depré, D; Chen, L; Ghosez, L. *Tetrahedron*, **2003**, *59*, 6797.

2.6.9. General procedure for the carboboration of *meso*-cyclobutenes.



An oven-dried vial was charged with $[Cu(CH_3CN)_4]PF_6$ (7.5 mg, 0.02 mmol, 10.0 mol%) and QuinoxP* (7.4 mg, 0.022 mmol, 11.0 mol%) and sealed with a septum. The vial was connected to an argon-vacuum line, evacuated and backfilled with argon (x3). THF (0.7 mL) was added and the mixture was stirred for 15 min at room temperature. With the vial still connected to the double line, the solvent was removed to dryness. Then, a solution of B_2pin_2 (2 equiv) in THF (1 mL) was added and the mixture was stirred for 15 min. A 0.2 M NaO*t*-Bu solution in THF (150 µL, 0.3 mmol, 1.5 equiv) was then added dropwise and the dark brown solution was stirred for 10 min. The reaction mixture was cooled at –78 °C for 10 min and the corresponding cyclobutene **II-1** (0.2 mmol, 1.0 equiv) was added followed by methyl iodine (50 µL, 0.8 mmol, 4.0 equiv). Then, the reaction mixture was stirred overnight (16 h) at the room temperature. Hexanes was added to the mixture and solvent was removed under reduced pressure. Crude was purified by flash column chromatography over silica gel (Eluent is indicated in each case).

(–)-2-((1*R*,2*S*,3*R*,4*S*)-2,3-Dibenzyl-4-methylcyclobutyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, **II-27d**.



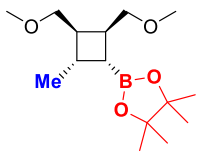
II-27d

From **II-1d** (46.9 mg, 0.2 mmol), following the general procedure described above and purifying crude by flash column chromatography over silica gel using *n*-pentane/ethyl ether 95:5 as eluent, compound **II-27d** (53 mg, 0.14 mmol) was obtained in 71% yield as a colorless oil.

[α]$^{20}_{D}$= –12.5 (*c* = 1.0, $CHCl_3$). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.15-7.35 (m,10H), 2.68-3 (m, 4H), 2.34-2.43 (m, 2H), 1.70-1.75 (m,1H), 1.30-1.35 (m, 1H), 1.16 (s, 6H), 1.12 (s, 6H), 0.9-0.94 (d, *J*= 6 Hz 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 141.2, 128.78, 128.75, 128.18, 128.15, 125.6, 125.5, 82.8, 45.7, 37.4, 36.2, 36.2, 33.9, 24.9, 24.8, 20.1 [note: the carbon attached to boron was not observed due to quadrupole broadening caused by the ^{11}B nucleus]. **HRMS-EI^{+}** m/z calculated for $C_{25}H_{33}BO_2$ [M+Na]+: 399.2450, found 399.2465.

Compound **II-27d** was transformed into **II-28** through oxidation followed by benzoylation to determine the enantiomeric ratio (See compound **II-28**).

(–)-2-((1*R*,2*S*,3*R*,4*S*)-2,3-bis(Methoxymethyl)-4-methylcyclobutyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, **II-27f**.



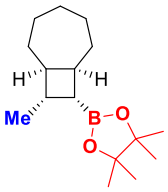
II-27f

From **II-1f** (28.4 mg, 0.2 mmol), following the general procedure described above and purifying crude by flash column chromatography over silica gel using *n*-pentane/ethyl ether 80:20 as eluent, compound **II-27f** (30 mg, 0.113 mmol) was obtained in 66% yield as a yellowish oil.

[α]$^{20}_{D}$= –14.1 (*c* = 1.0, $CHCl_3$). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 3.52 – 3.45 (m, 2H), 3.40 – 3.31 (m, 2H), 3.29 (s, *J* = 1.8 Hz, 3H), 3.28 (s, 3H), 2.74 – 2.59 (m, 1H), 2.38 – 2.23 (m, 2H), 1.64 – 1.54 (m, 1H), 1.23 (s, *J* = 2.7 Hz, 6H), 1.22 (s, 6H), 1.10 (d, *J* = 6.6 Hz, 3H).**^{13}C NMR** (75 MHz, $CDCl_3$): δ 83.6, 83.2, 74.1, 73.3, 58.8, 58.6, 43.3, 34.1, 32.8, 25.1, 25.1, 25.0, 19.7. [note: the carbon attached to boron was not observed due to quadrupole broadening caused by the ^{11}B nucleus]. **HRMS-ESI^{+}** m/z calculated for $C_{15}H_{30}BO_4$ [M+H]+: 285.2244, found 285.2237.

Compound **II-27f** was transformed into **II-29f** through oxidation followed by benzoylation to determine the enantiomeric ratio (See compound **II-29f**).

(–)-4,4,5,5-Tetramethyl-2-((1*R*,7*S*,8*R*,9*S*)-9-methylbicyclo[5.2.0] nonan-8-yl)-1,3,2-dioxaborolane, **II-27g**.



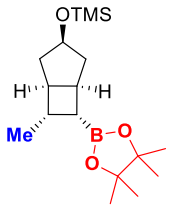
II-27g

From **II-1g** (24.4 mg, 0.2 mmol), following the general procedure described above and purifying crude by flash column chromatography over silica gel using *n*-pentane/ethyl ether 90:10 as eluent, compound **II-27g** (35.4 mg, 0.13 mmol) was obtained in 67% yield as a yellowish oil.

[α]$^{20}_{D}$= –15.9 (*c* = 1.0, $CHCl_3$). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 2.49 – 2.35 (m, 1H), 2.17 – 1.94 (m, 2H), 1.77 (m, 3H), 1.64 (m, 2H), 1.54 – 1.31 (m, 3H), 1.26 (s, 6H), 1.25 (s, 6H), 1.19 – 1.11 (m, 1H), 1.06 (m, 5H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 83.0, 46.4, 36.7, 34.7, 34.2, 32.6, 29.9, 29.3, 25.2, 25.1, 24.9, 20.0. [note: the carbon attached to boron was not observed due to quadrupole broadening caused by the ^{11}B nucleus]. **HRMS-EI^{+}** m/z calculated for $C_{16}H_{29}BO_2$ [M+Na]+: 287.2162, found 287.2152.

Compound **II-27g** was transformed into **II-29g** through oxidation followed by benzoylation to determine the enantiomeric ratio (See compound **II-29g**).

(–)-(1*S*,3*R*,5*S*,6*R*)-6-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)bicyclo[3.2.0]heptan-3-ol, **II-2j**.



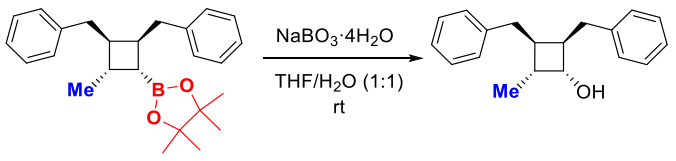
II-27m

From **II-1m** (36.4 mg, 0.2 mmol), following the general procedure described above by flash column chromatography over silica gel using *n*-pentane/ethyl ether 90:10 as eluent, compound **II-27m** (35.7 mg, 0.11 mmol) was obtained in 55% yield as a yellowish oil.

[α]$^{20}_{D}$= –11.7 (*c* = 1.0, $CHCl_3$). **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 4.35 – 4.24 (m, 1H), 2.72 – 2.62 (m, 1H), 2.57 – 2.41 (m, 1H), 2.21 (m,1H), 2.00 – 1.82 (m, 3H), 1.72 – 1.59 (m, 2H), 1.28 (s, 6H), 1.27 (s, 6H), 1.17 – 1.05 (d, *J* = 7 Hz, 3H), 0.10 (s, 9H). **^{13}C-NMR** (75 MHz, $CDCl_3$) δ 77.3, 45.5, 43.5, 42.6, 35.6, 34.6, 25.3, 25.1, 21.2, 0.3. **HRMS-EI+** m/z calculada para $C_{17}H_{33}O_3Si$ [M+Na]+: 347.2188, encontrada 347.2145.

2.6.10. Derivatizations to determine the enantiomeric excess of cyclobutylboronates **II-27d**, **II-27f** and **II-27g**.

*2.6.10.1. Synthesis of (–)-(1R,2R,3R,4R)-2,3-dibenzyl-4-methylcyclobutan-1-ol, **II-28**.*

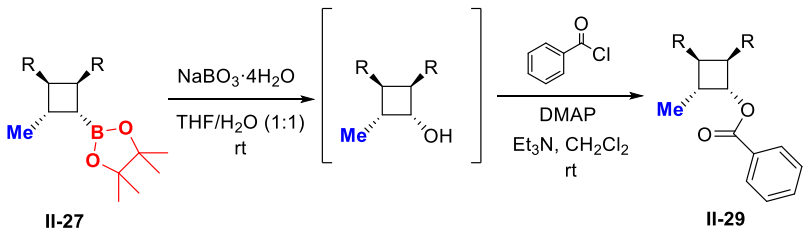


II-27d **II-28**

$NaBO_3 \cdot 4H_2O$ (4 equiv) was added to a solution of **II-27d** (38 mg, 0.1 mmol, 1 equiv) in THF/H_2O (1:1, 10.8 mL/mmol cyclobutylboronate). The reaction mixture was stirred overnight at room temperature and then quenched with H_2O and extracted with Et_2O (x3). The combined organic phases were washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuum to afford the alcohol. The residue was purified by flash column chromatography on silica gel using hexanes/ Et_2O 80:20 as eluent. Compound **II-28** (23 mg, 0.9 mmol) was obtained in 87% yield as a yellow oil.

$[\alpha]^{20}_D$= –31.6 (*c* = 1.0, $CHCl_3$). Compound **II-28** was obtained with a 92:8 enantiomeric ratio determined by SFC using Chiralpak-IB column [CO_2/MeOH (80:20)], 2.0 mL/min, τ_{major}= 3.5 min, τ_{minor}= 3.9 min. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.28-7.05 (m, 10H), 4.18-4.09 (m, 1H), 2.89-2.82 (m, 1H), 2.82-2.76 (m, 2H), 2.71-2.50 (m, 2H), 2.25-2.11 (m, 2H), 1.36 (s, 1H), 0.91-0.89 (d, *J* = 6 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 141.0, 140.9, 128.6, 128.5, 128.5, 128.3, 125.9, 125.8, 71.2, 46.5, 39.6, 37.9, 36.3, 34.8, 13.5. **HRMS-ESI$^+$** m/z calculated for $C_{19}H_{22}O$ [M+Na]+: 289.1574, found 289.1572.

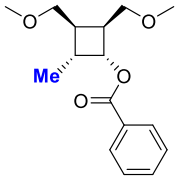
*2.6.10.2. Procedure for synthesis of benzoates **II-29**.*



$NaBO_3 \cdot 4H_2O$ (4 equiv) was added to a solution of the corresponding cyclobutylboronate **II-27** (1 equiv) in THF/H_2O (1:1, 10.8 mL/mmol cyclobutylboronate). The reaction mixture was stirred overnight at room temperature and then quenched with H_2O and extracted with Et_2O (x3). The combined organic phases were washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuum to afford the alcohol. This compound was used in the next step without further purification.

To a solution of corresponding alcohol in CH_2Cl_2, 4-dimethylaminopyridine (DMAP) (2.1 equiv), triethylamine (3 equiv) and the corresponding benzyl chloride (2.0 equiv) were added. The reaction mixture was stirred for 30 min at room temperature and then quenched with H_2O. The aqueous layer was extracted with Et_2O (x3) and the combined organic phases were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel.

(–)-(1*R*,2*S*,3*R*,4*R*)-2,3-bis(Methoxymethyl)-4-methylcyclobutyl benzoate, **II-29f**.

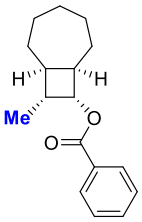


II-29f

From **II-27f** (31 mg, 0.11 mmol), following the general procedure described above, purifying crude by flash column chromatography over silica gel using *n*-pentane/ethyl ether 70:30 as eluent, compound **II-29f** (21 mg, 0.08 mmol) was obtained in 73% global yield as a yellow oil.

[α]$^{20}_{D}$= –46.1 (*c* = 1.0, $CHCl_3$). Compound **II-29f** was obtained with a 91:9 enantiomeric ratio determined by SFC using Chiralpak-IA column [CO_2/MeOH (95:5)], 1.0 mL/min, τ_{major}= 8.8 min, τ_{minor}= 7.9 min. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.11 – 7.87 (m, 1H), 7.55 – 7.42 (m, 1H), 7.40 – 7.29 (m, 1H), 5.22 – 5.01 (m, 1H), 3.58 – 3.39 (m, 4H), 3.29 (s, 3H), 3.27 (s, 3H), 2.98-2.83 (m, 1H), 2.53 (m, 1H), 2.28 – 1.99 (m, 1H), 1.08 (d, *J* = 7.3 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 166.3, 133.0, 130.4, 129.7, 128.5, 72.8, 71.7, 71.3, 62.9, 58.9, 58.9, 41.5, 38.7, 35.5, 14.5. **HRMS-ESI$^+$** m/z calculated for $C_{16}H_{23}O_4$ [M+H]+: 279.1595, found 279.1596.

(–)-(1*R*,7*R*,8*R*,9*R*)-9-Methylbicyclo[5.2.0]nonan-8-yl benzoate, **II-29g**.



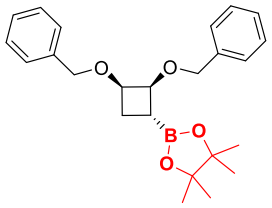
II-29g

From **II-27g** (29 mg, 0.11 mmol), following the general procedure described above, purifying crude by flash column chromatography over silica gel using *n*-pentane/ethyl ether 90:10 as eluent, compound **II-29g** (23 mg, 0.09 mmol) was obtained in 82% global yield as a yellowish oil.

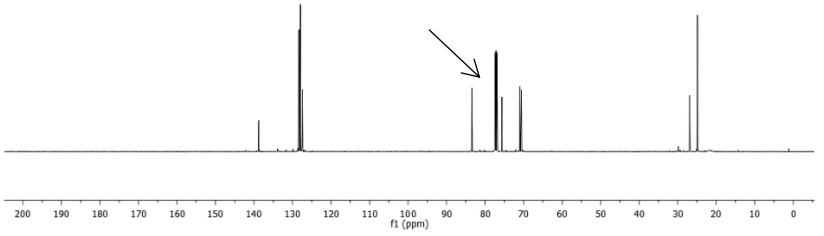
[α]$^{20}_{D}$= –31.6 (*c* = 1.0, $CHCl_3$). Compound **II-29g** was obtained with a 88:12 enantiomeric ratio determined by SFC using Chiralpak-IA column [CO_2/MeOH (99:1)], 1.0 mL/min, τ_{major}= 20.7 min, τ_{minor}= 24.9 min. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.14 – 7.99 (m, 2H), 7.62

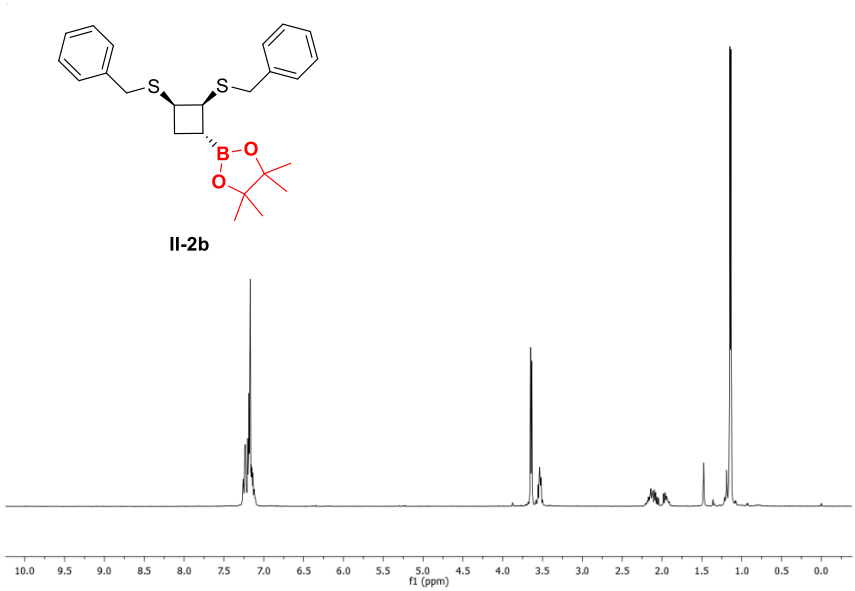
– 7.51 (m, 1H), 7.48 – 7.40 (m, 2H), 5.00 (m, 1H), 2.71 (m, 1H), 2.43 – 2.27 (m, 1H), 2.08 – 1.96 (m, 2H), 1.92 – 1.72 (m, 4H), 1.65 – 1.45 (m, 2H), 1.47 – 1.22 (m, 3H), 1.23 – 1.15 (m, 1H), 1.17 – 0.92 (m, 5H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 166.5, 132.9, 130.8, 129.7, 128.4, 75.8, 43.3, 42.4, 37.3, 32.5, 32.5, 31.1, 30.3, 28.6, 14.8. **HRMS-EI$^+$** m/z calculated for $C_{17}H_{22}O_2$ [M+Na]+: 281.1525, found 281.1512.

2.7. NMR Spectra.

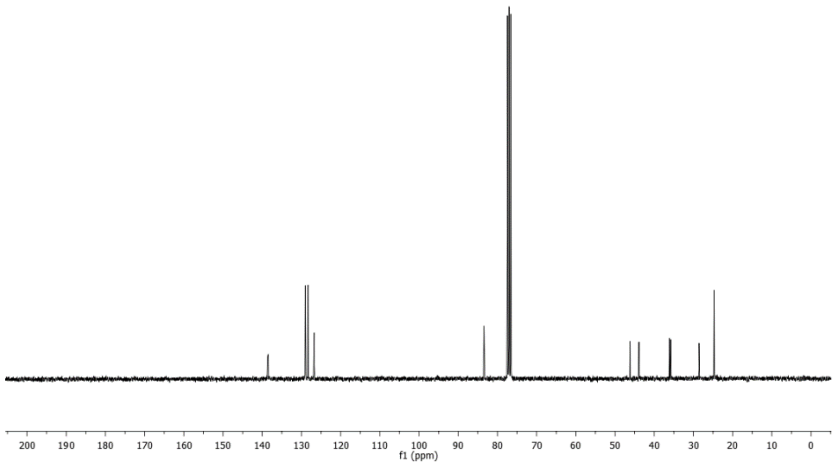


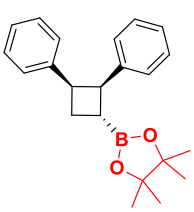
II-2a




S
S
B
O
O
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

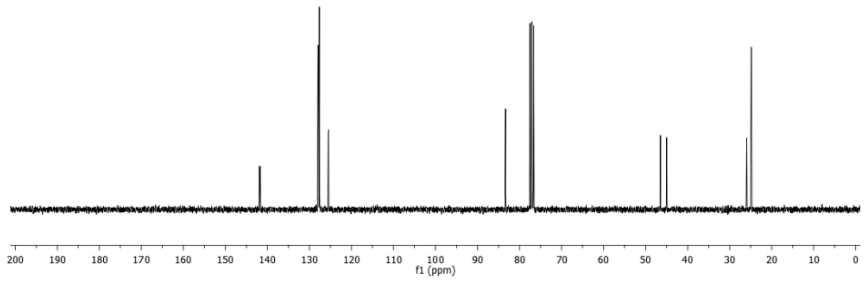
II-2b


200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


B
O
O

II-2c

7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)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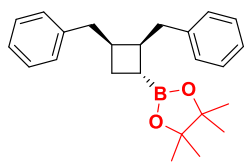
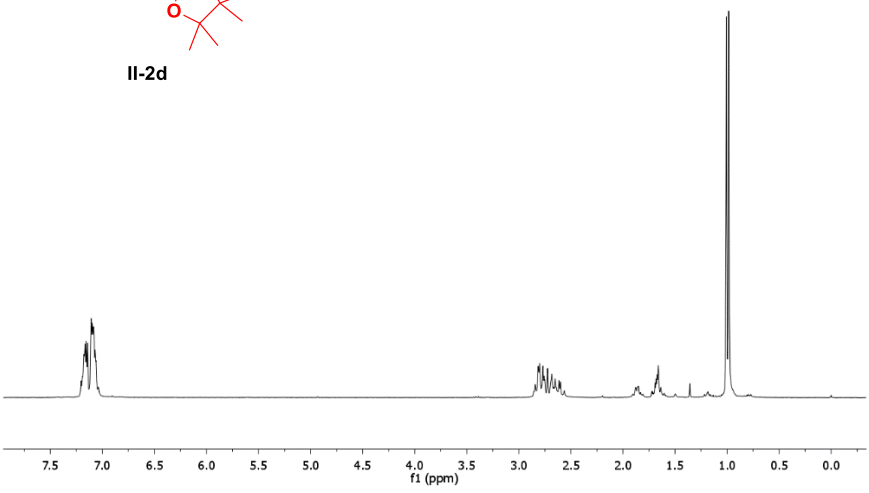
f1 (ppm)


B
O
O

II-2d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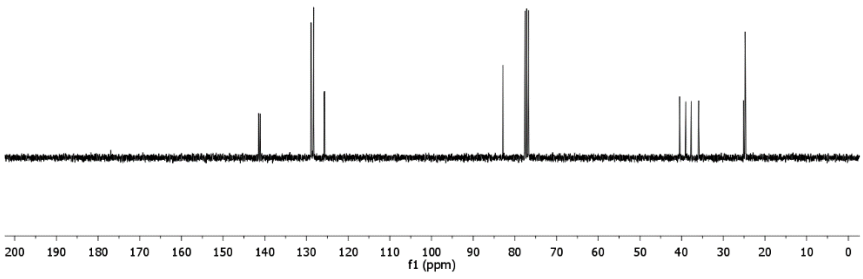
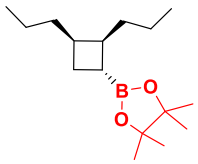
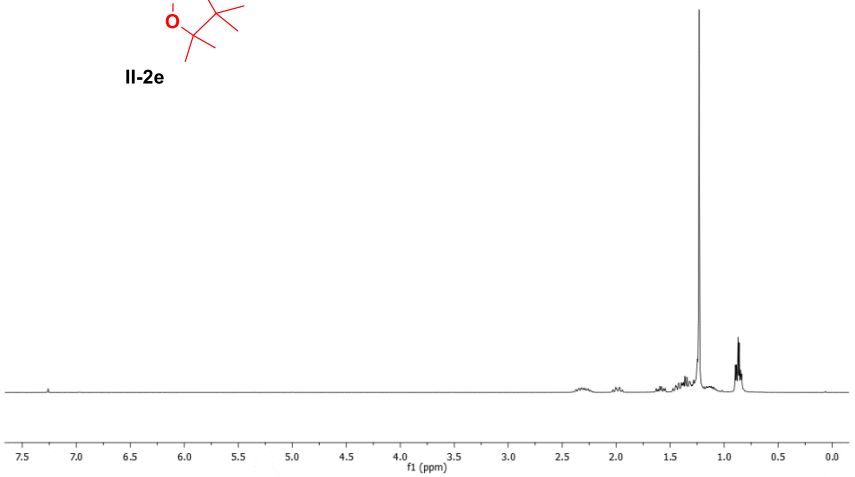
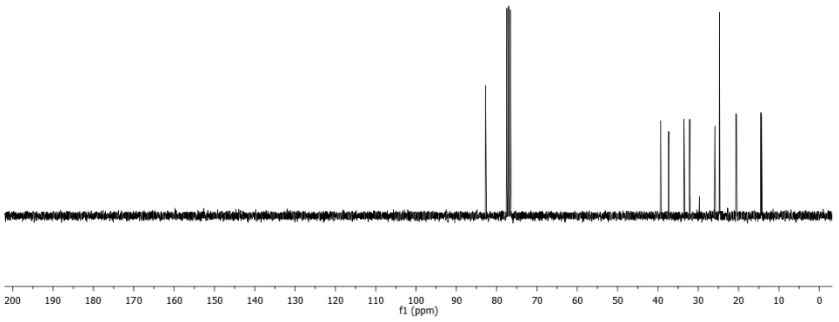
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

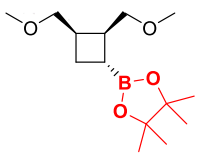

200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


B
O
O

II-2e

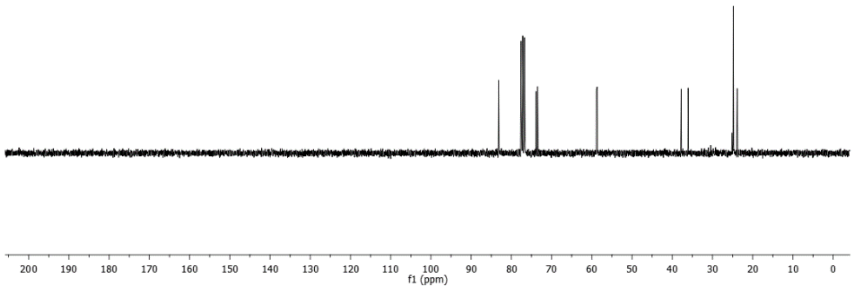

7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

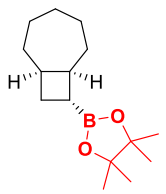

200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


O
O
B
O
O

II-2f

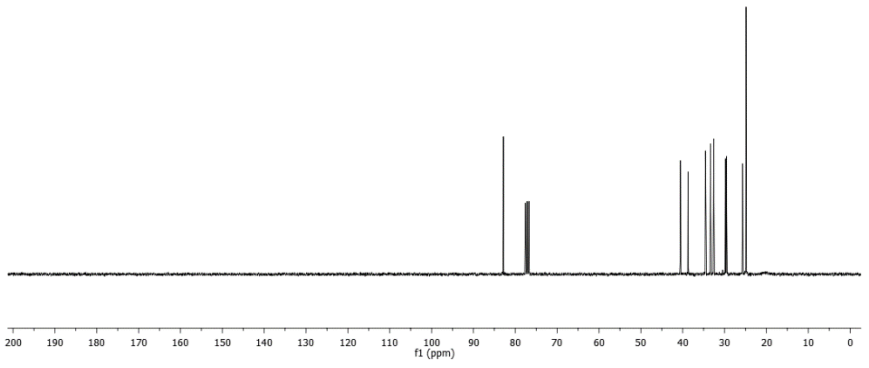
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

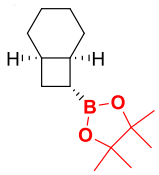

200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


H
H
B
O
O

II-2g

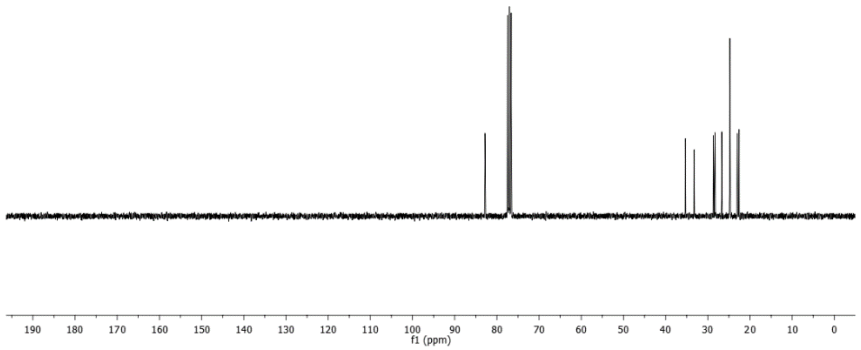
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

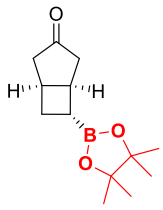

200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


H
H
B
O
O

II-2h

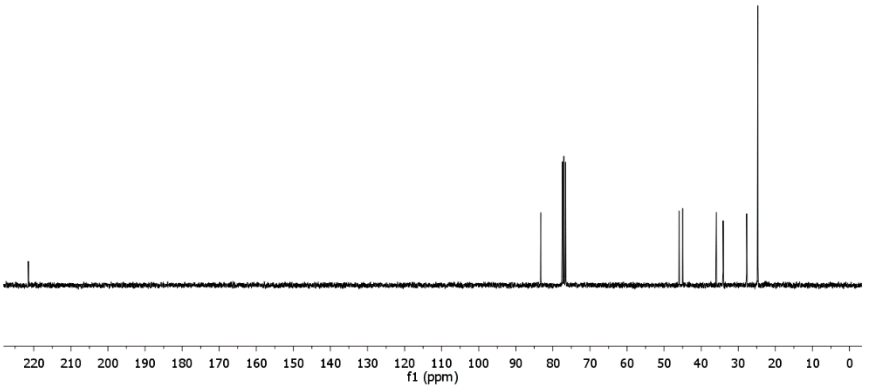
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

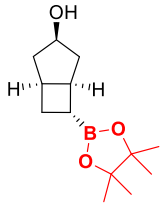

190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


O
H
H
B
O
O

II-2i

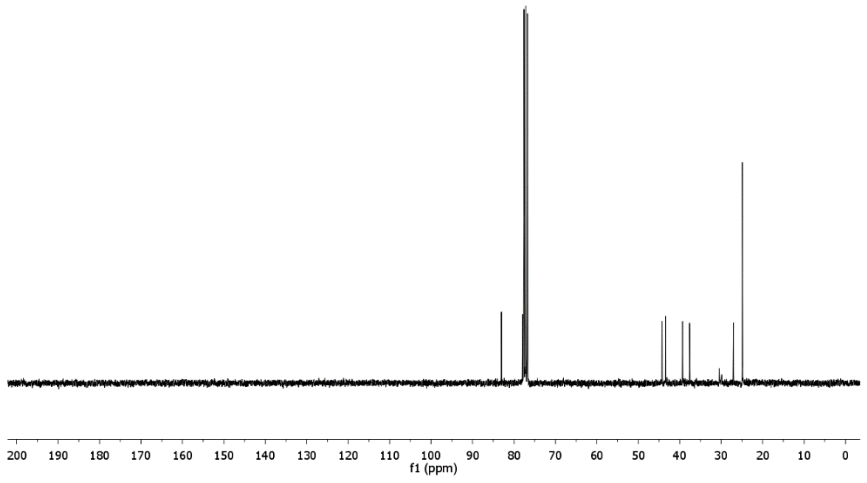
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

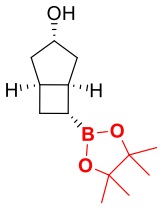

220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


OH
H
H
B
O
O

II-2j

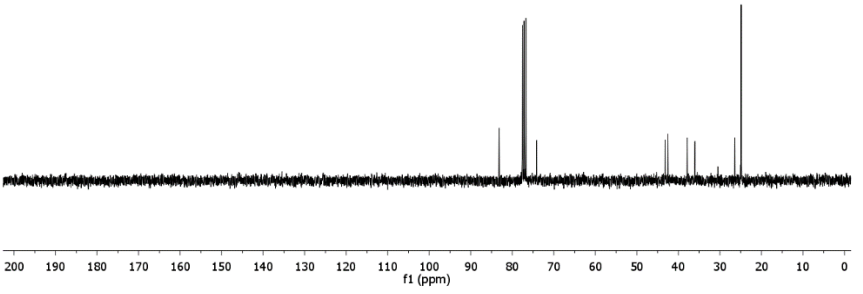
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

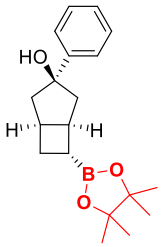

200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


OH
H
H
B
O
O

II-2k

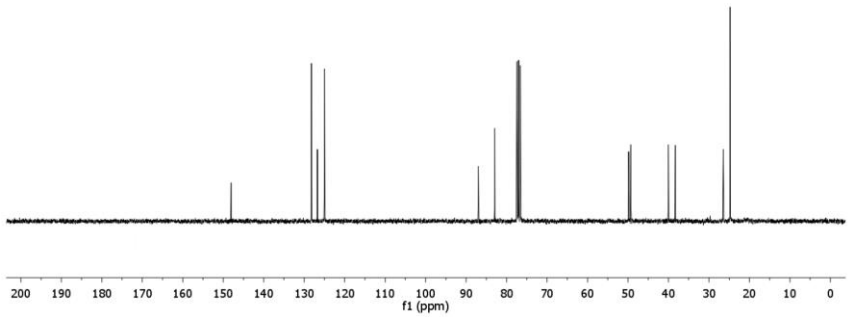
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

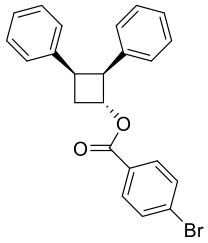

200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


HO
H
H
B
O
O

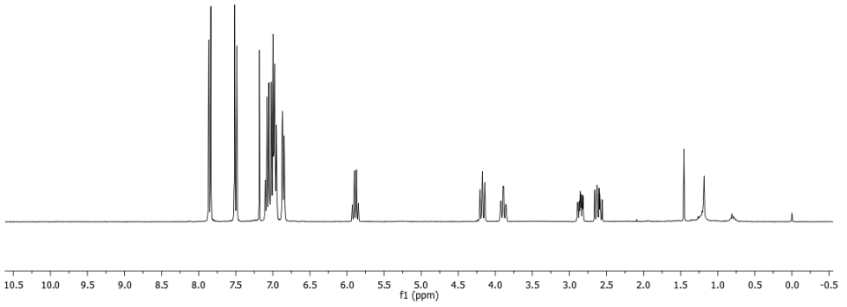
II-2l

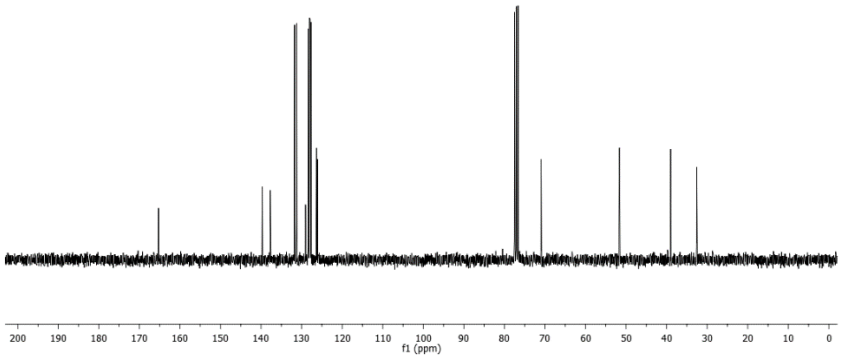
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

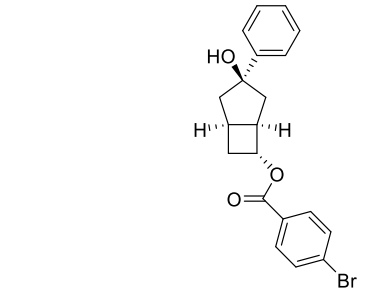

200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


O
O
Br

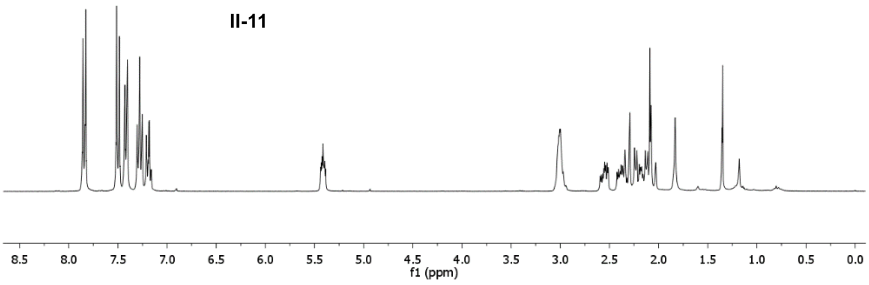
II-10

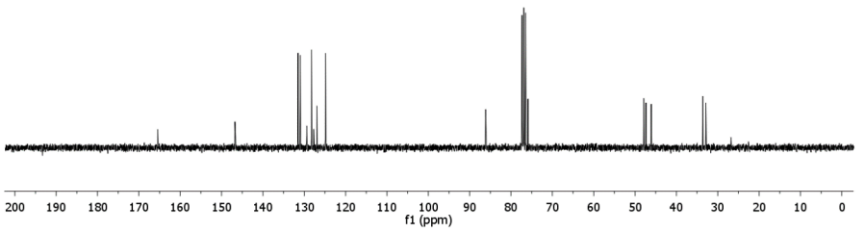

10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

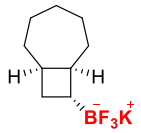

200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


HO
H
H
O
O
Br

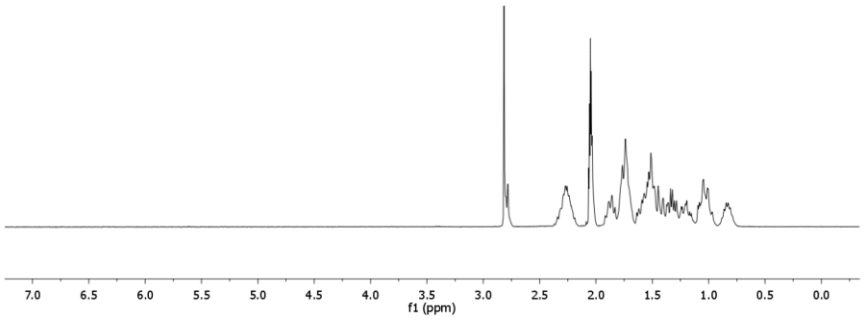
II-11

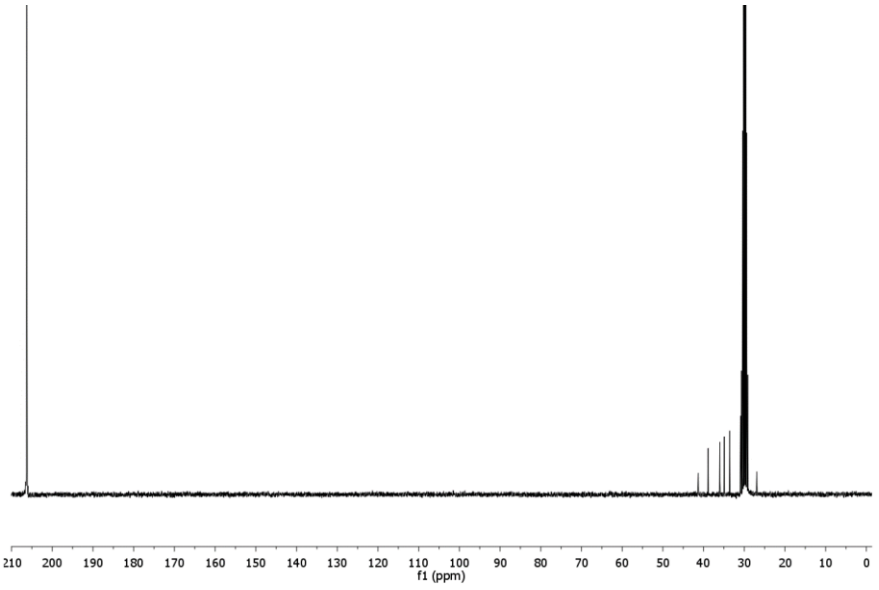

8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

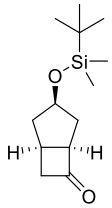

200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


H
H
BF3K

II-12

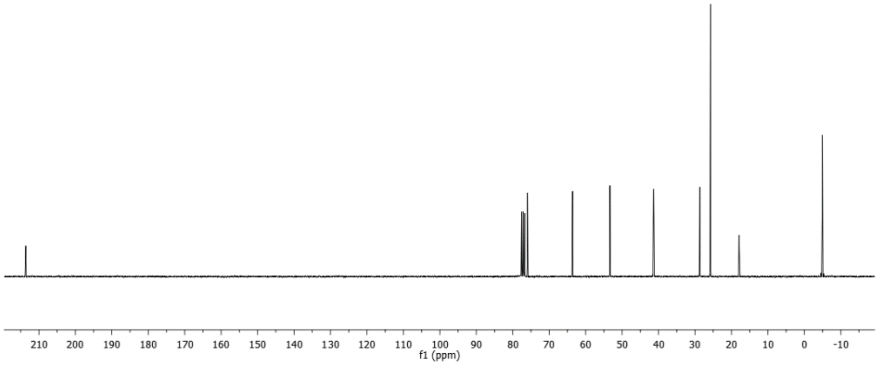

7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

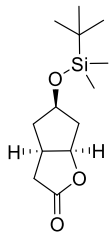

210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


Si
O
H
H
O

II-14

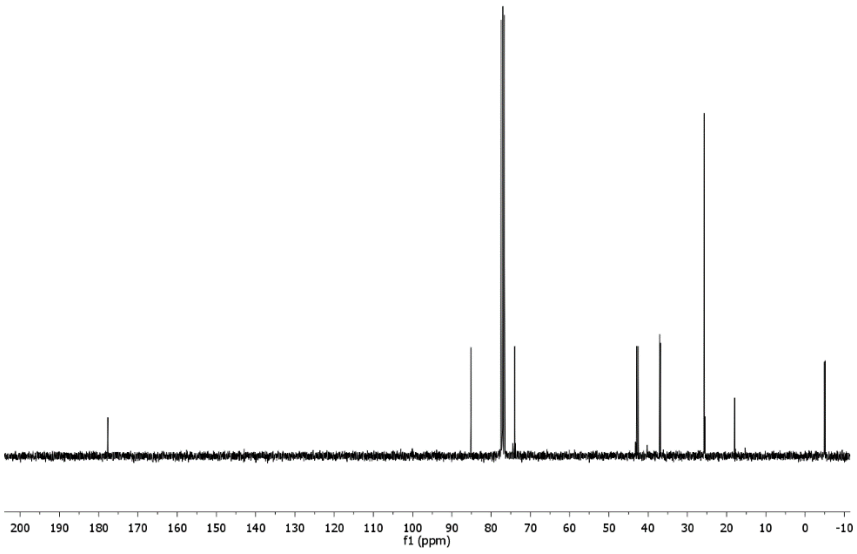
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

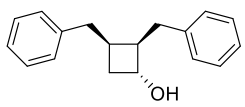

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


Si
O
H
H
O
O

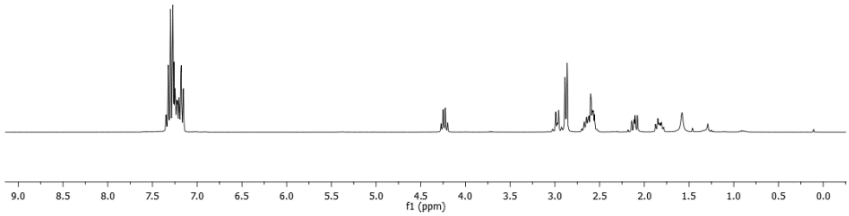
II-17

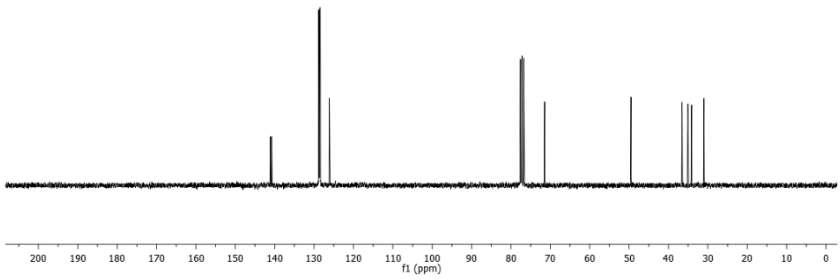
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

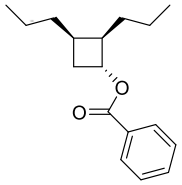

200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


OH

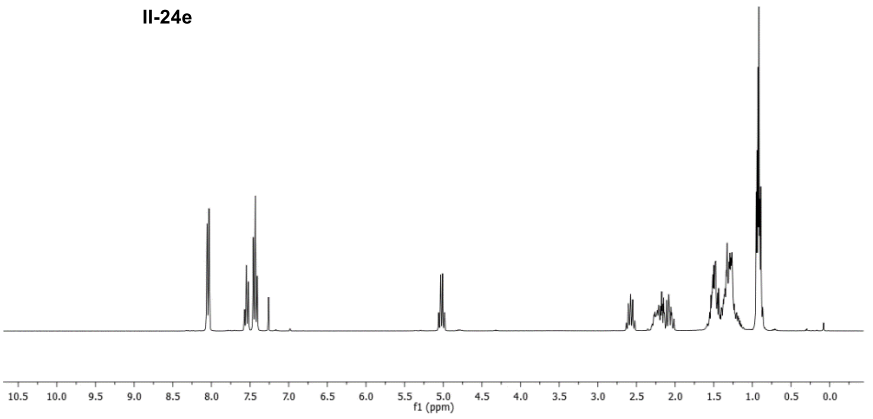
II-23

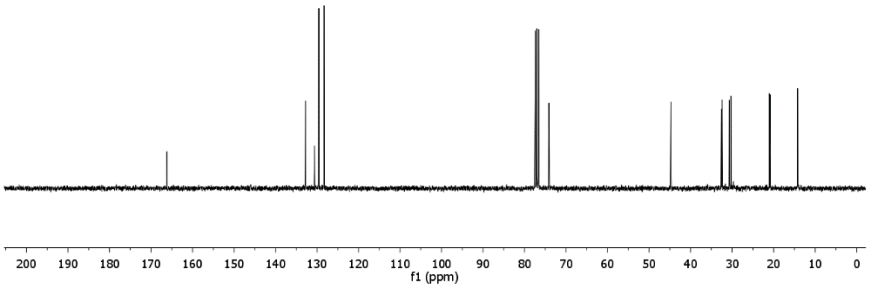

9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

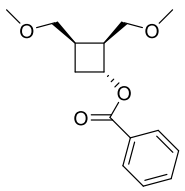

200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)



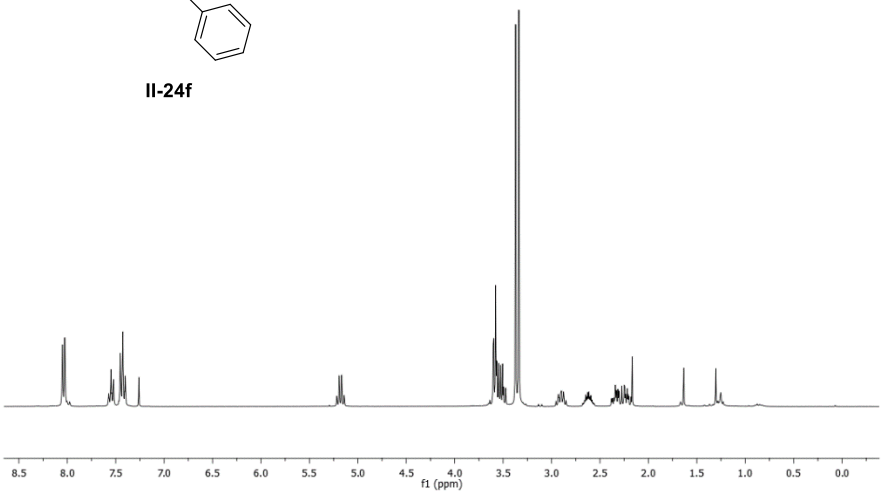
II-24e

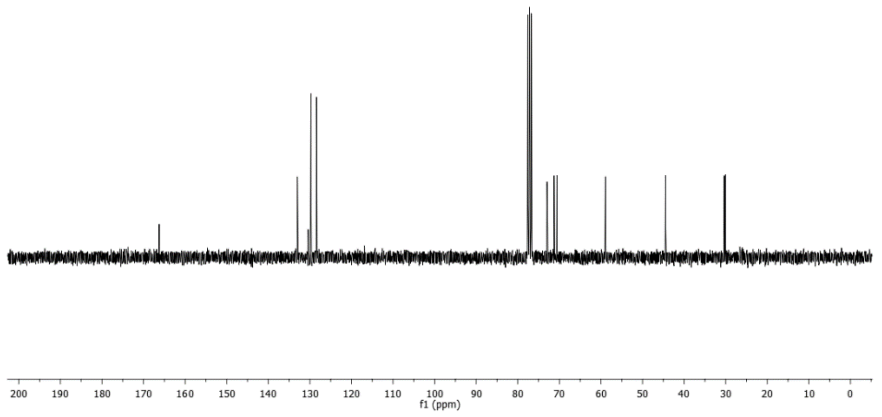

10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

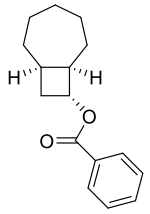

200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)



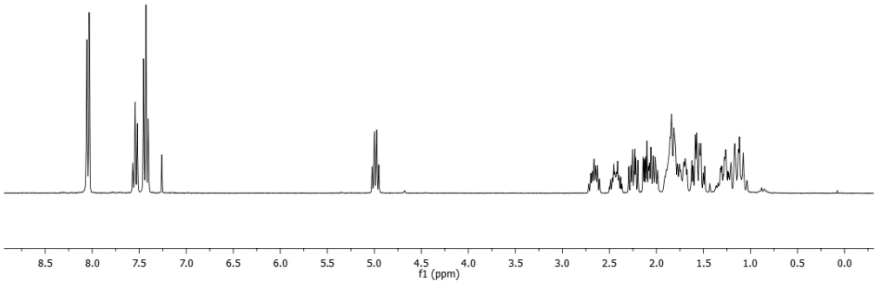
II-24f

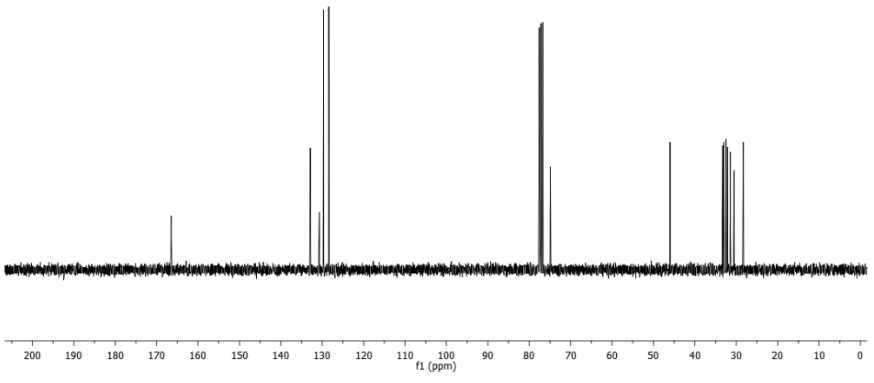

8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

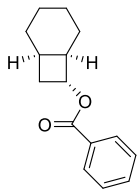

200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


H
H
O
O

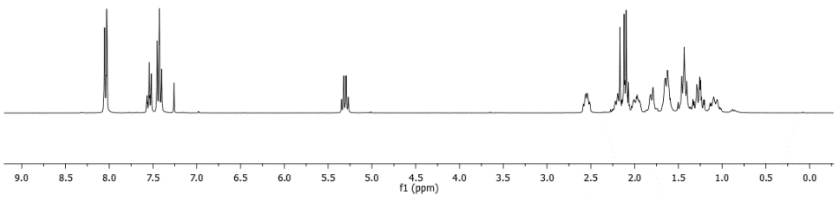
II-24g

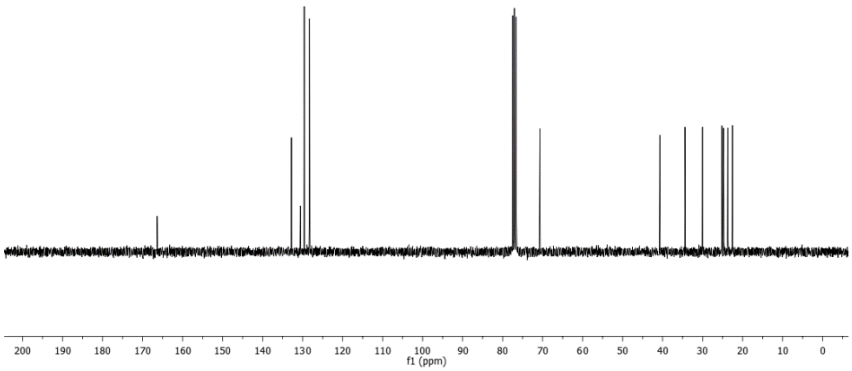

8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

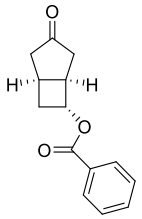

200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


H
H
O
O

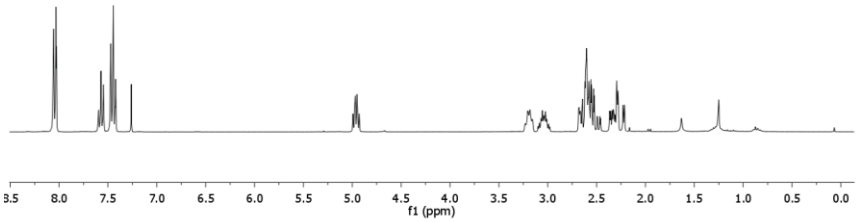
II-24h

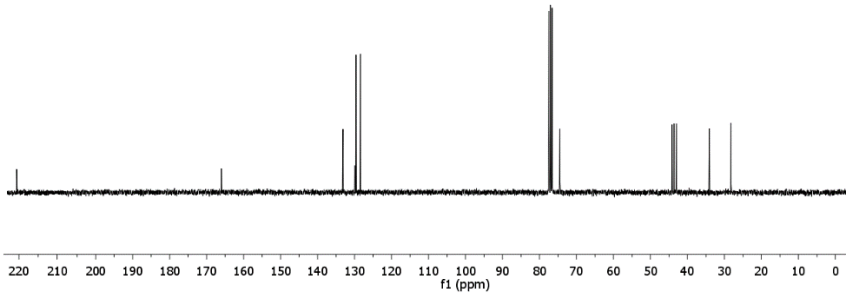

9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

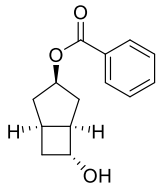

200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)



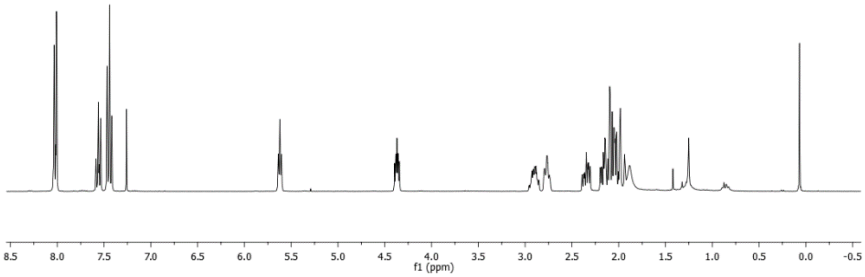
II-24i

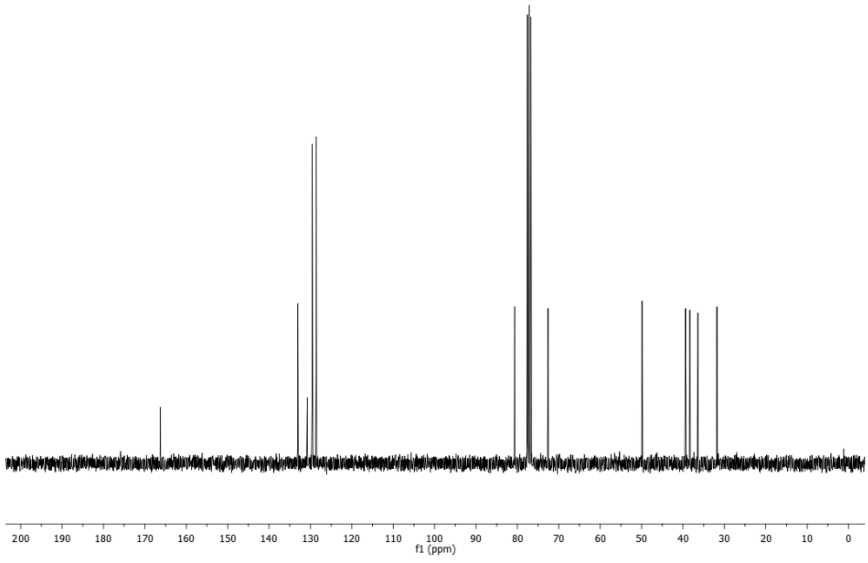

3.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

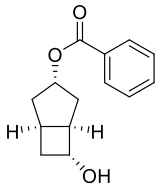

220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


O
O
H
H
OH

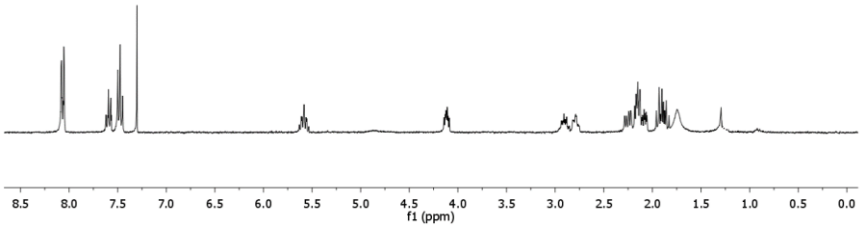
II-25j

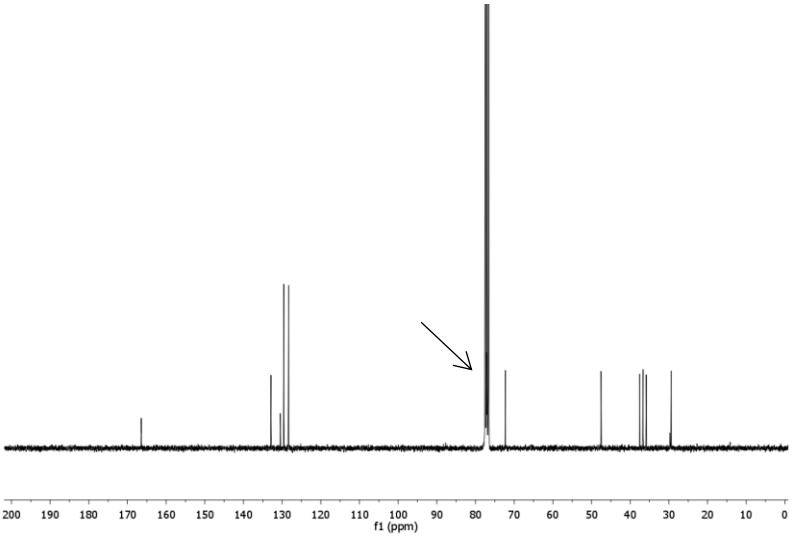

8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

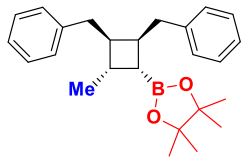

200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


O
O
H
H
OH

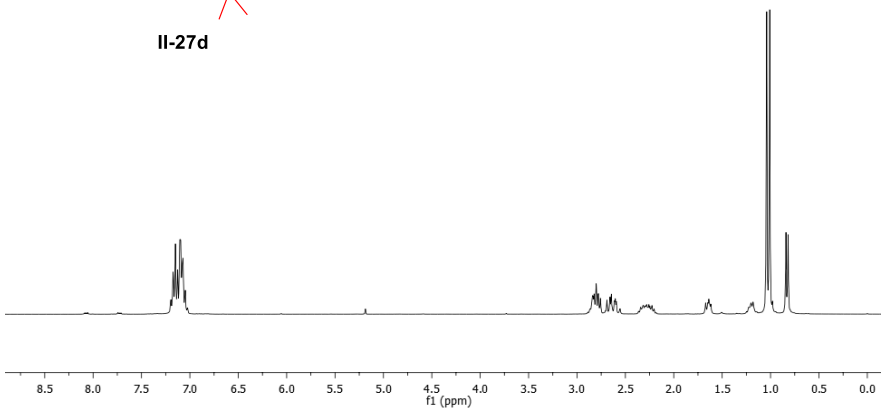
II-25k

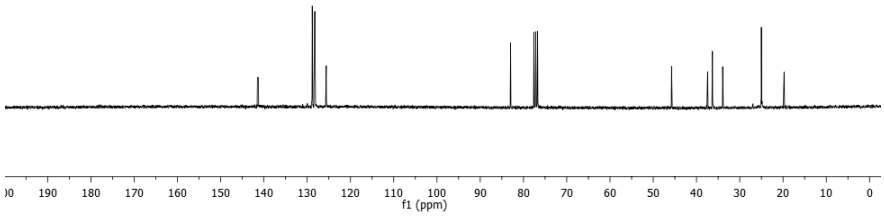

8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

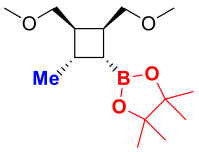

200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


Me
B
O
O

II-27d

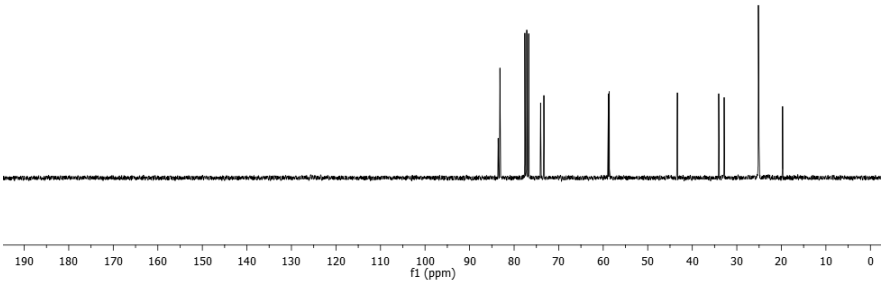

8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

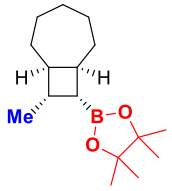

190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


O
O
Me
B
O
O

II-27f

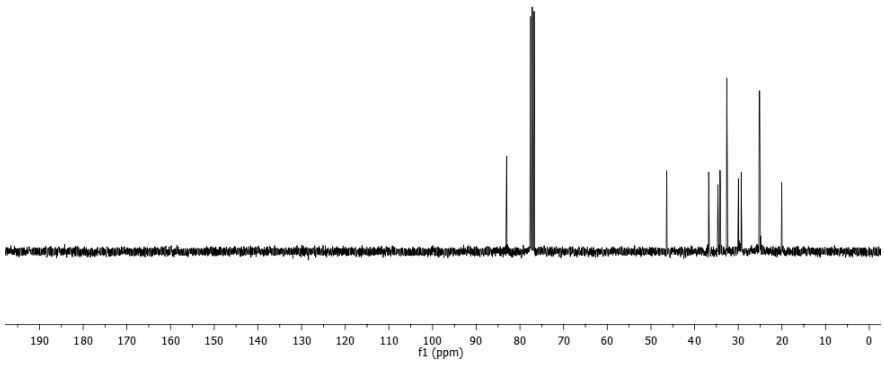
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

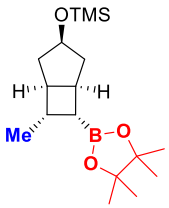

190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


H
H
Me
B
O
O

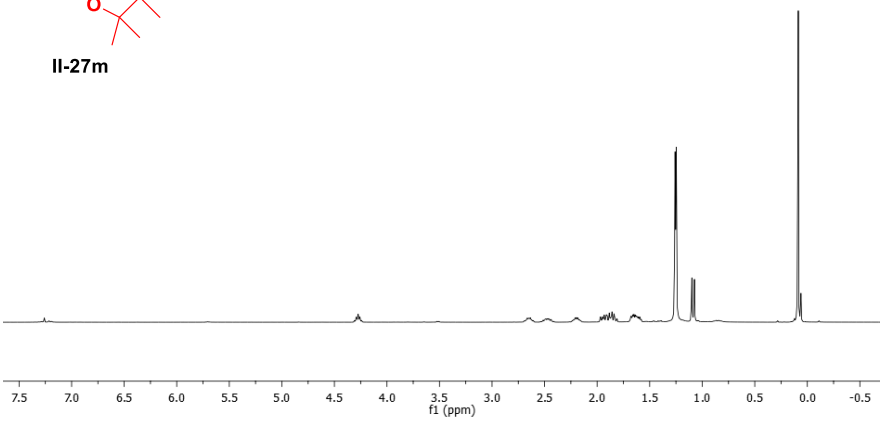
II-27g

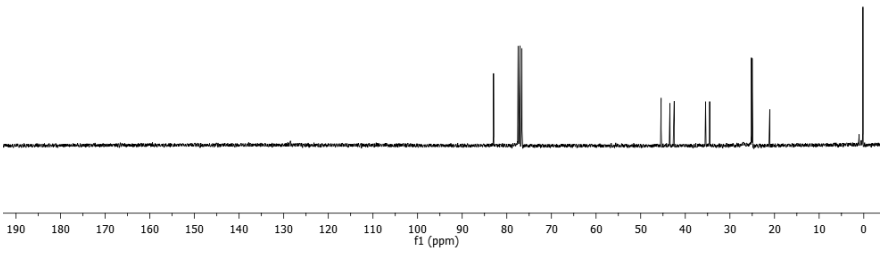
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

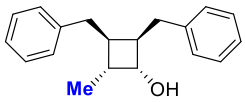

190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

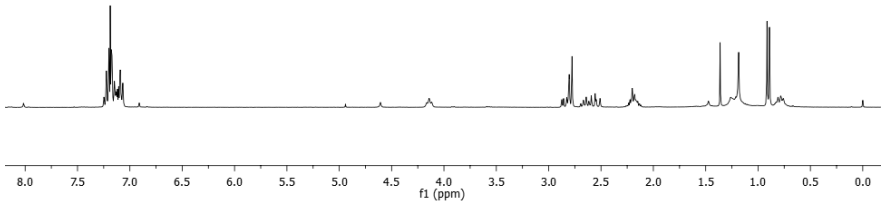

OTMS
H
H
Me
B
O
O

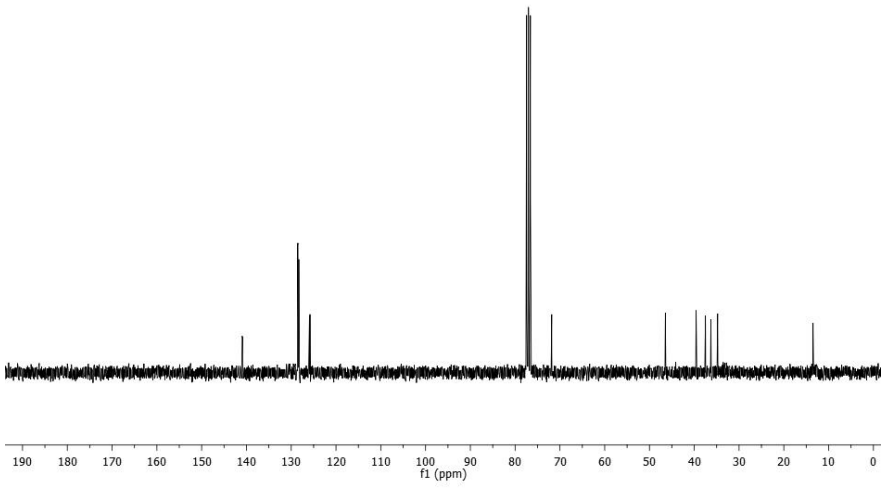
II-27m

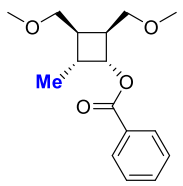

7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)


190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

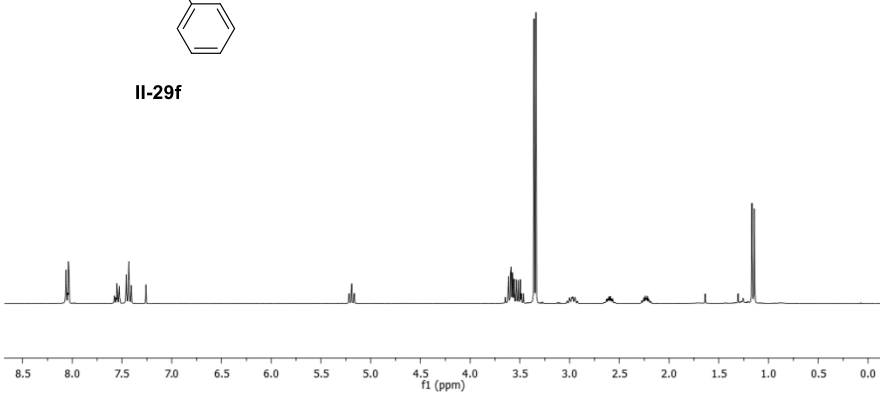

Me
OH

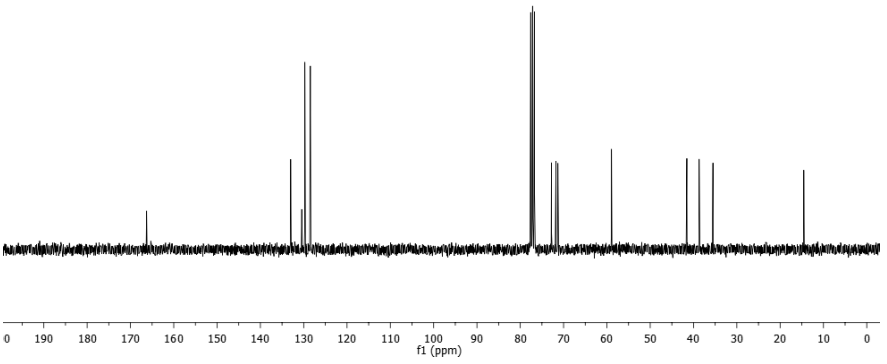

8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

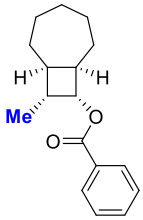

190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


O
O
Me
O
O

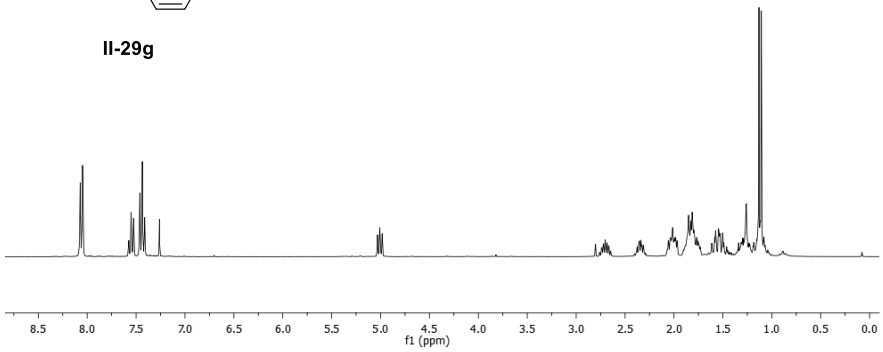
II-29f

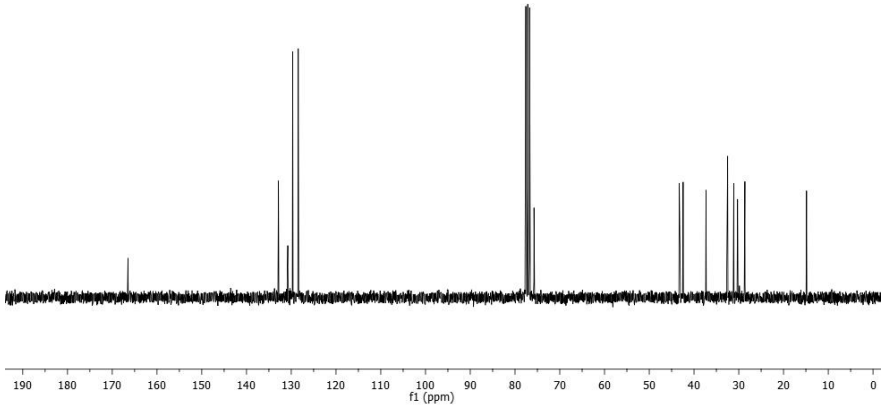

8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


0
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

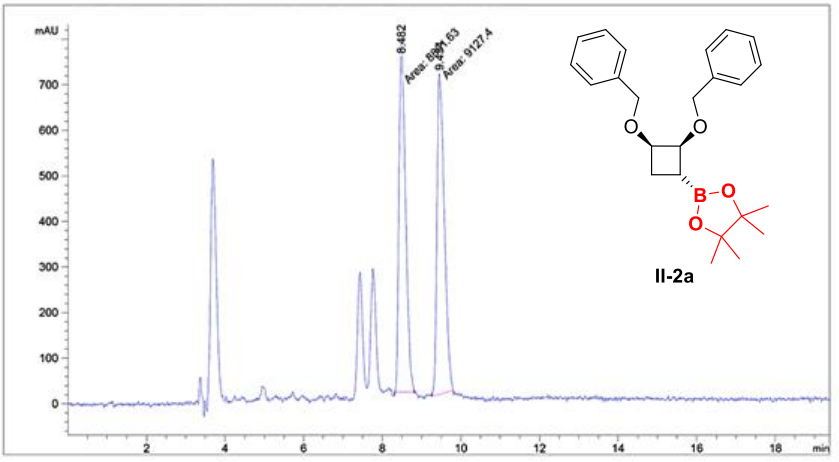

H
H
Me
O
O

II-29g

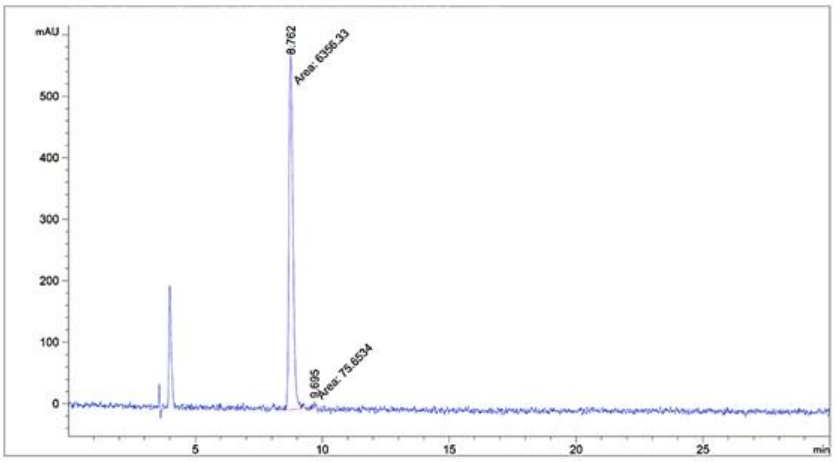

8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

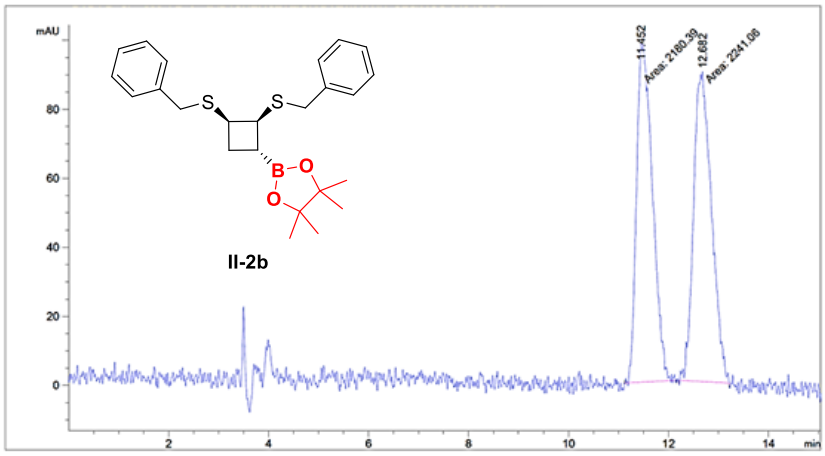
2.8. HPLC chromatograms.



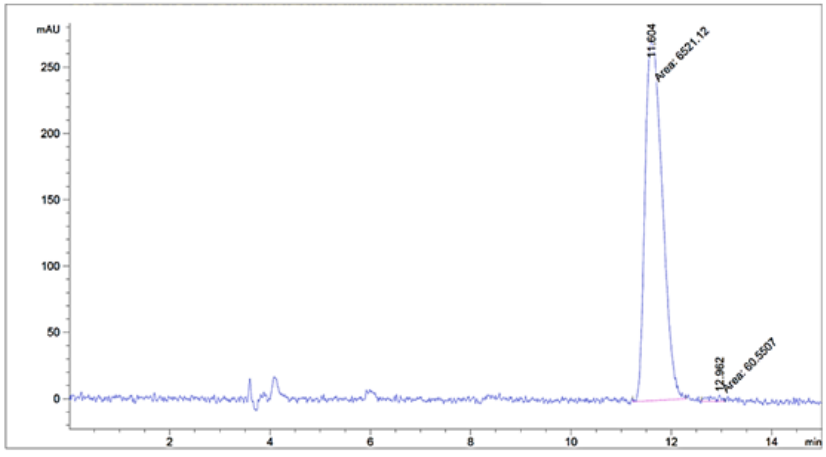
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.482	MM	0.1929	8861.63281	765.64246	49.2613
2	9.454	MM	0.2161	9127.40430	703.92255	50.7387



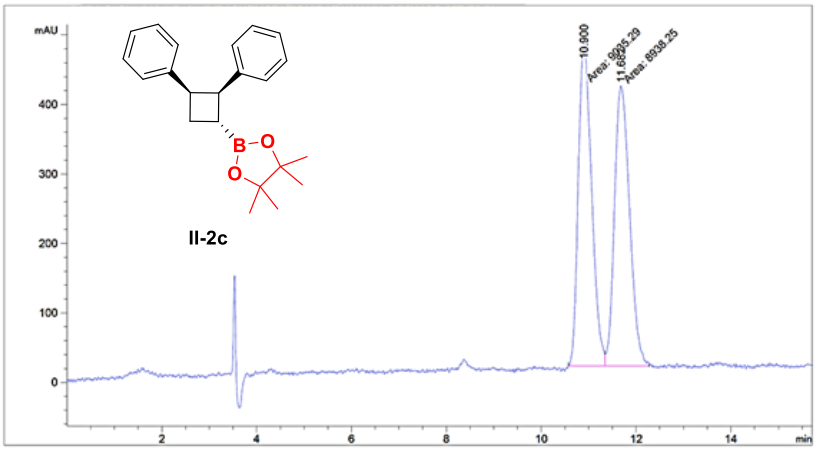
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.762	MM	0.1782	6356.32959	594.55292	98.8238
2	9.695	MM	0.1058	75.65338	11.91678	1.1762



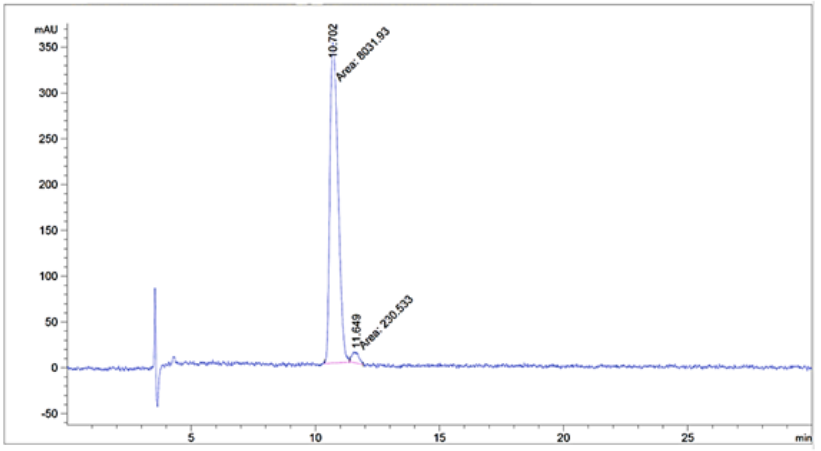
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.452	MM	0.3701	2180.39380	98.19816	49.3139
2	12.682	MM	0.4155	2241.06470	89.89304	50.6861



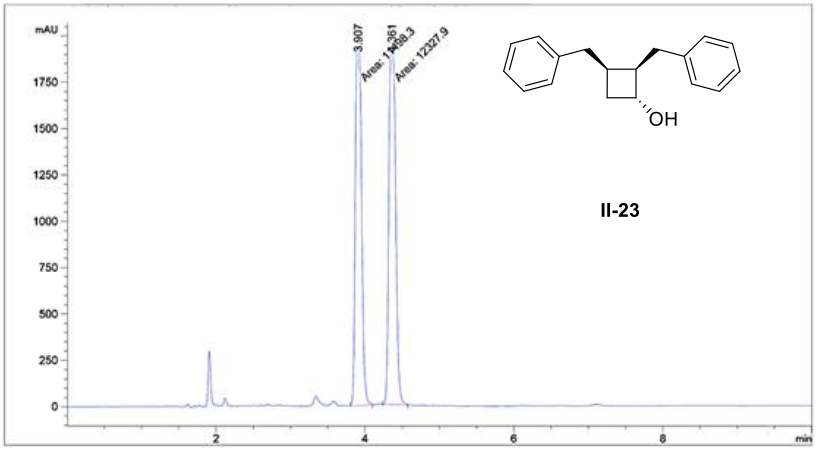
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.604	MM	0.4015	6521.11914	270.70499	99.0800
2	12.962	MM	0.2109	60.55067	4.78571	0.9200



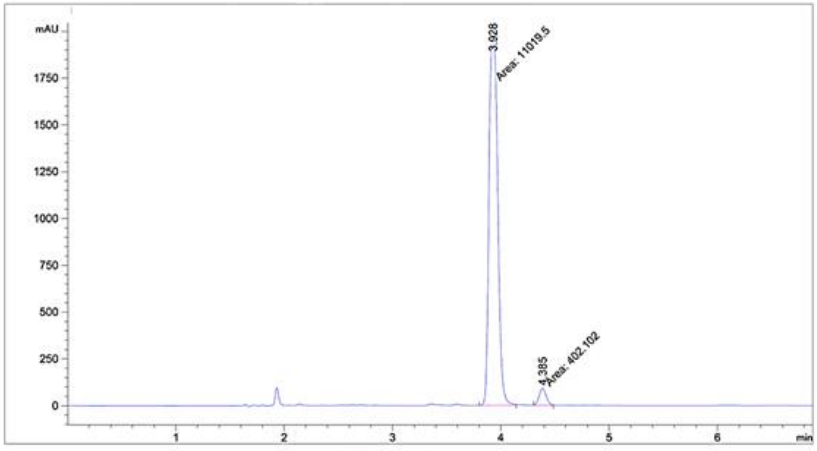
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.900	MF	0.3237	9035.29395	465.19031	50.2700
2	11.682	FM	0.3695	8938.24805	403.16324	49.7300



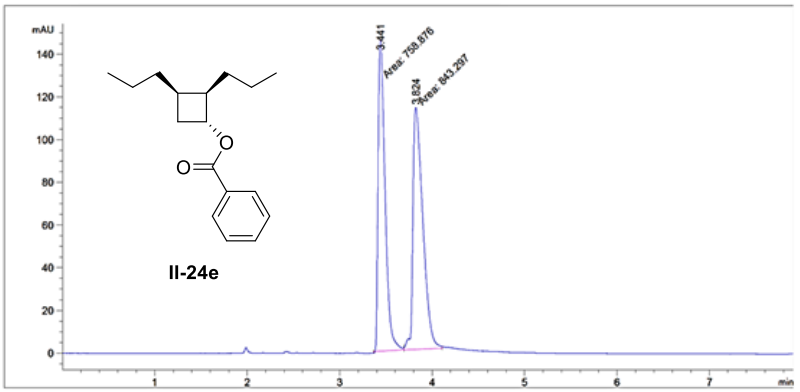
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.702	MM	0.3817	8031.92725	350.72876	97.2099
2	11.649	MM	0.3094	230.53259	12.41788	2.7901



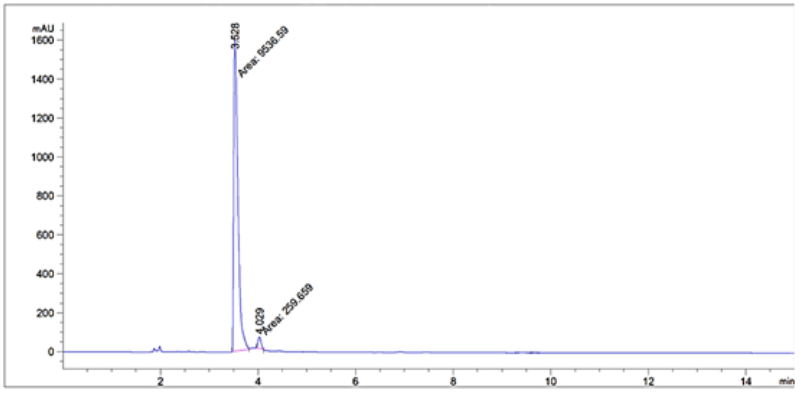
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.907	MM	0.0977	1.14983e4	1962.35693	48.2591
2	4.361	MM	0.1060	1.23279e4	1938.30652	51.7409



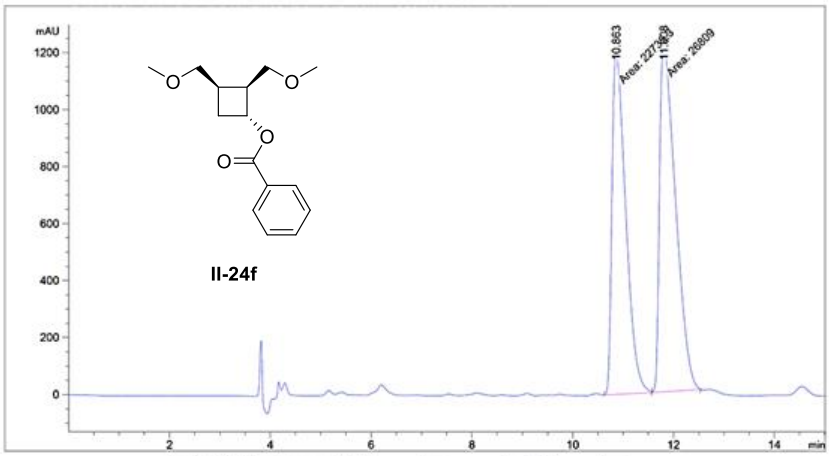
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.928	MM	0.0944	1.10195e4	1945.88489	96.4795
2	4.385	MM	0.0749	402.10233	89.42013	3.5205



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.441	MF	0.0867	758.87640	145.92662	47.3654
2	3.824	FM	0.1240	843.29718	113.35144	52.6346

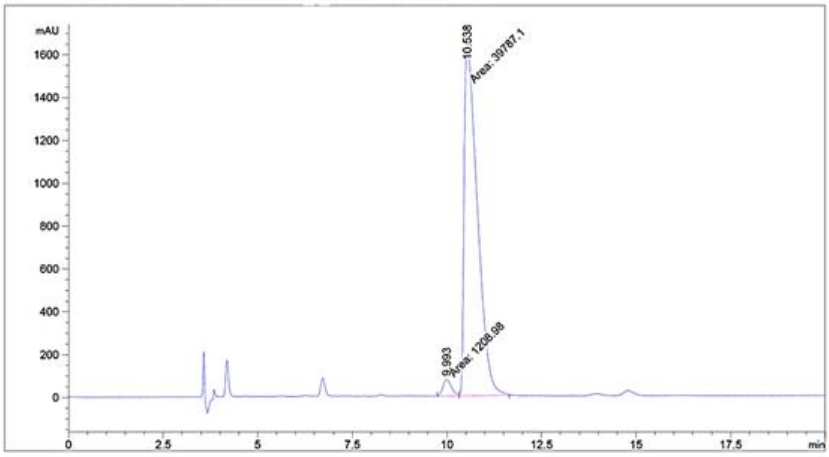


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.528	MM	0.0989	9536.59473	1606.51660	97.3494
2	4.029	MM	0.0733	259.65945	59.01505	2.6506

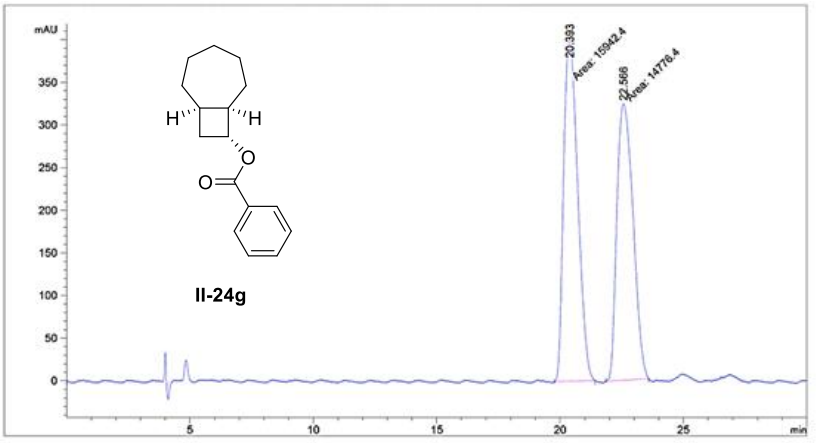


II-24f

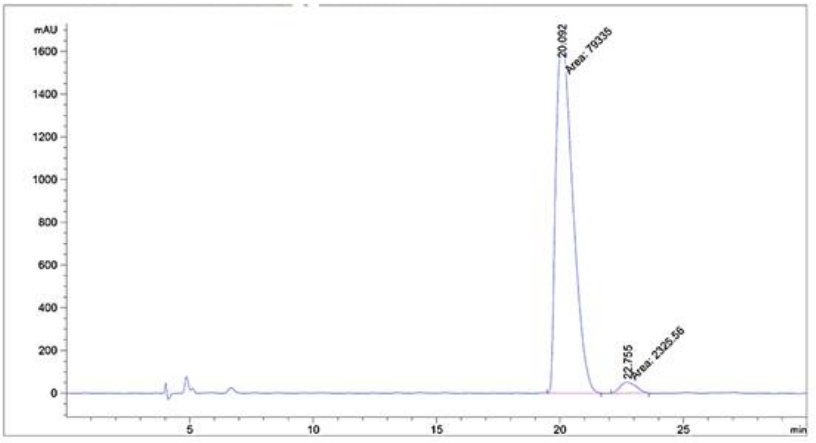
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.863	MM	0.3159	2.27353e4	1199.37891	45.8889
2	11.808	MM	0.3655	2.68090e4	1222.60181	54.1111



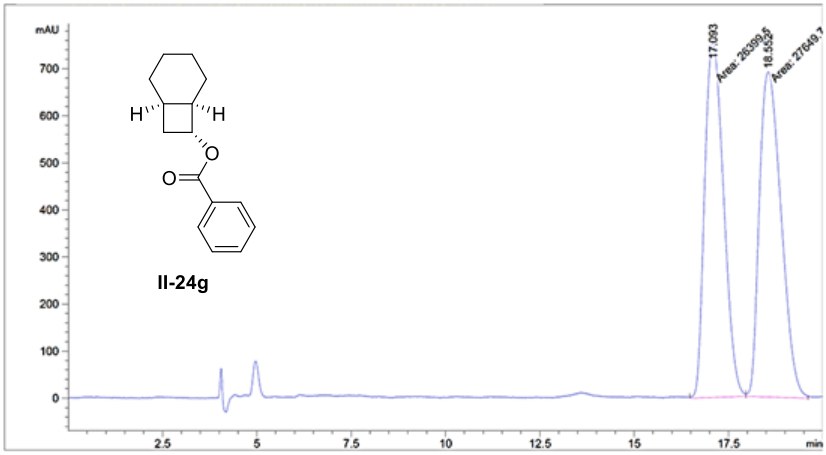
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.993	MF	0.2569	1208.98120	78.42951	2.9490
2	10.538	FM	0.4027	3.97871e4	1646.85034	97.0510



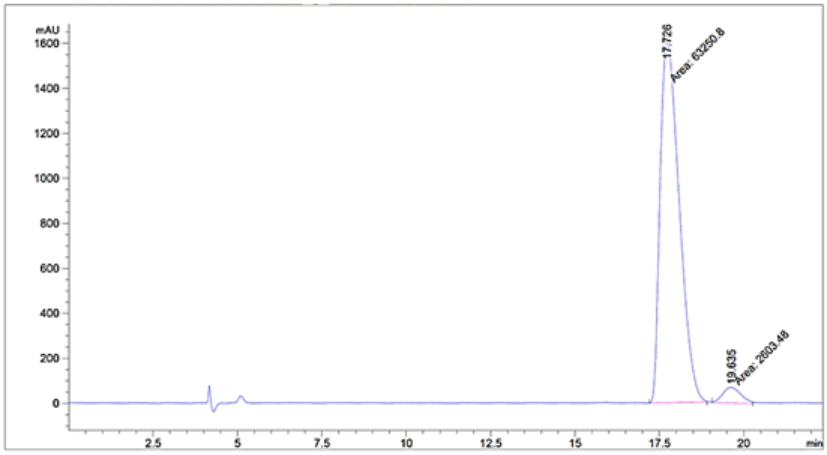
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	20.393	MM	0.6672	1.59424e4	398.26840	51.8979
2	22.566	MM	0.7594	1.47764e4	324.32080	48.1021



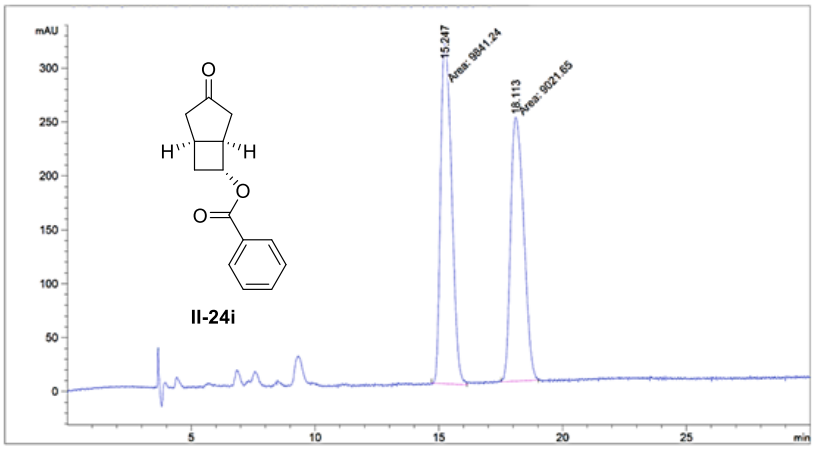
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	20.092	MM	0.8038	7.93350e4	1644.96643	97.1522
2	22.755	MM	0.7518	2325.55591	51.55863	2.8478



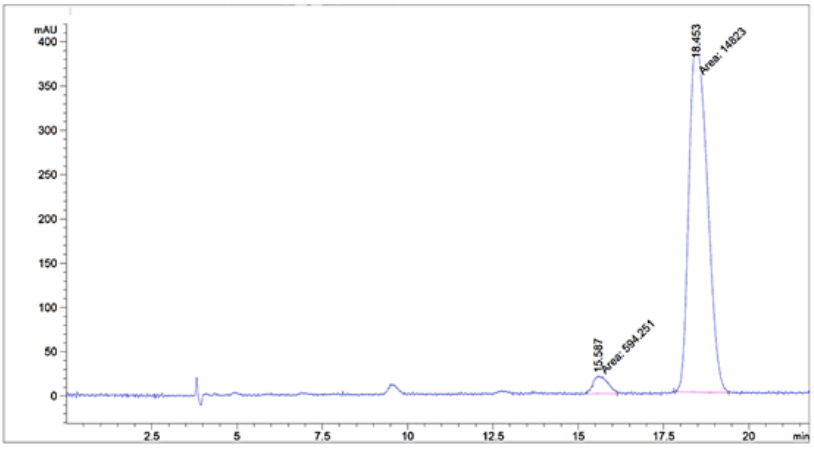
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.093	MM	0.5828	2.63995e4	754.98535	48.8435
2	18.552	MM	0.6666	2.76497e4	691.27985	51.1565



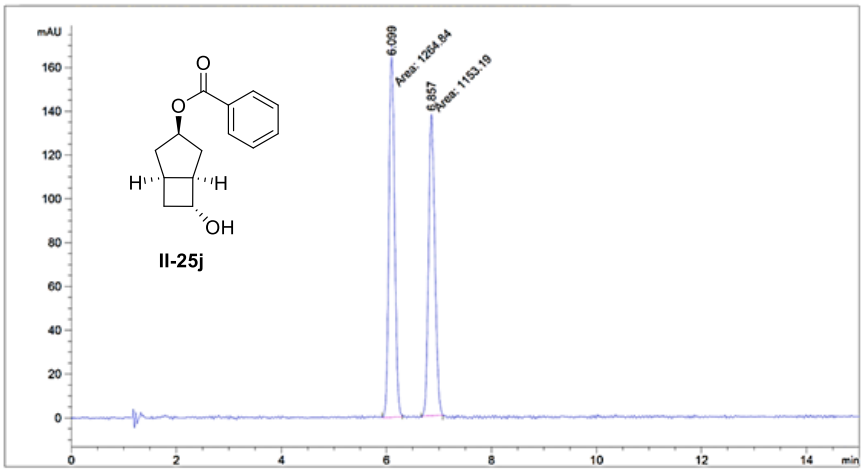
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.726	MM	0.6583	6.32508e4	1601.45911	96.0466
2	19.635	MM	0.6253	2603.48218	69.39368	3.9534



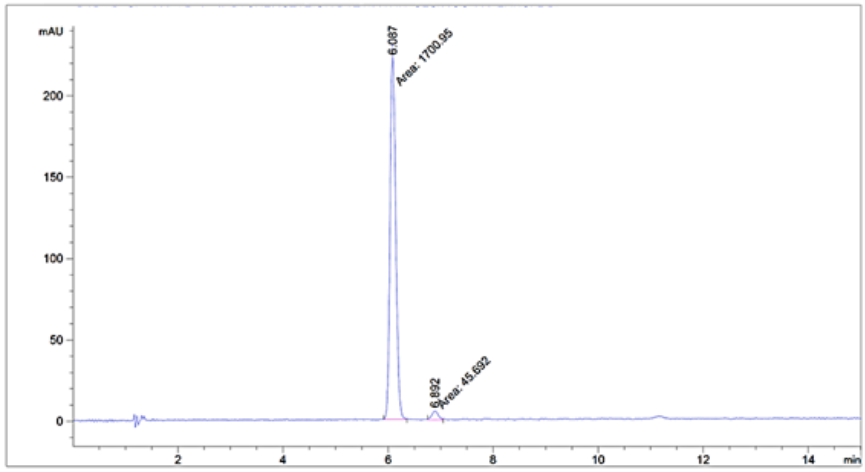
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.247	MM	0.5186	9841.23535	316.25427	52.1725
2	18.113	MM	0.6145	9021.65137	244.67175	47.8275



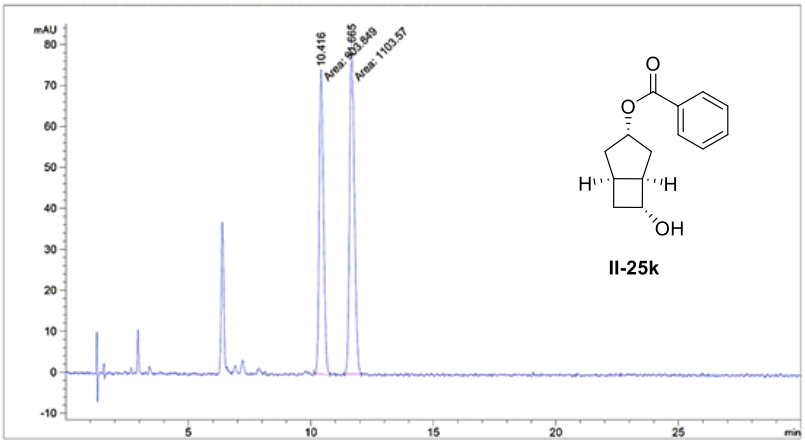
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.587	MM	0.4917	594.25110	20.14079	3.8545
2	18.453	MM	0.6250	1.48230e4	395.29871	96.1455



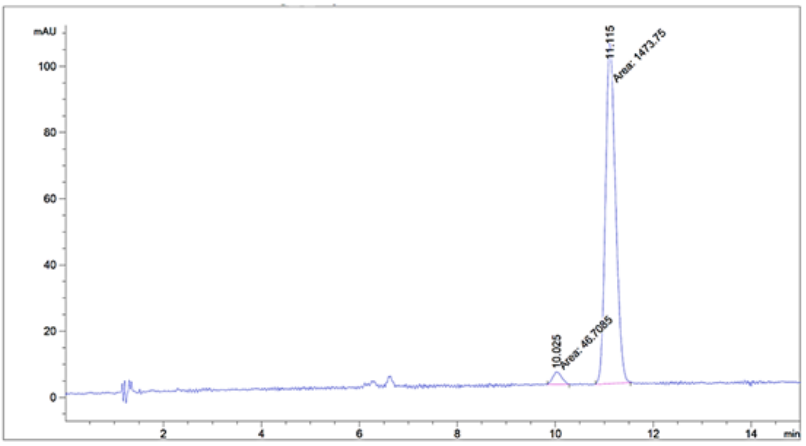
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.099	MM	0.1239	1264.84412	170.18312	52.3088
2	6.857	MM	0.1396	1153.19043	137.67090	47.6912



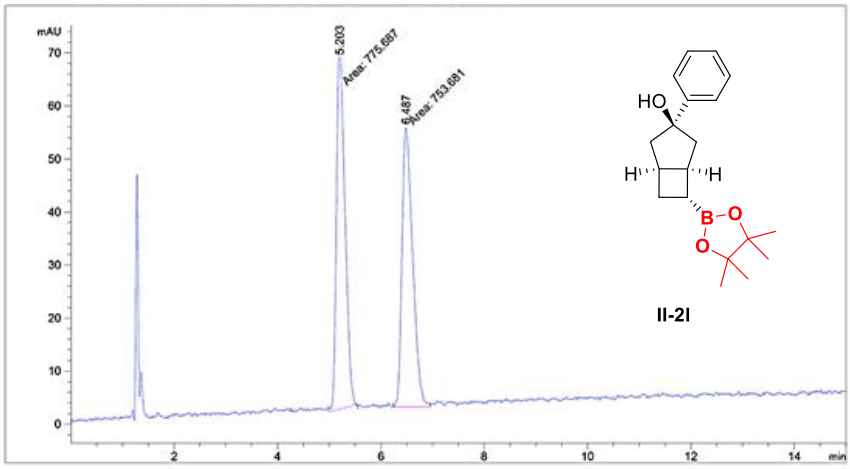
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.087	MM	0.1230	1700.95288	230.49297	97.3840
2	6.892	MM	0.1426	45.69204	5.34201	2.6160



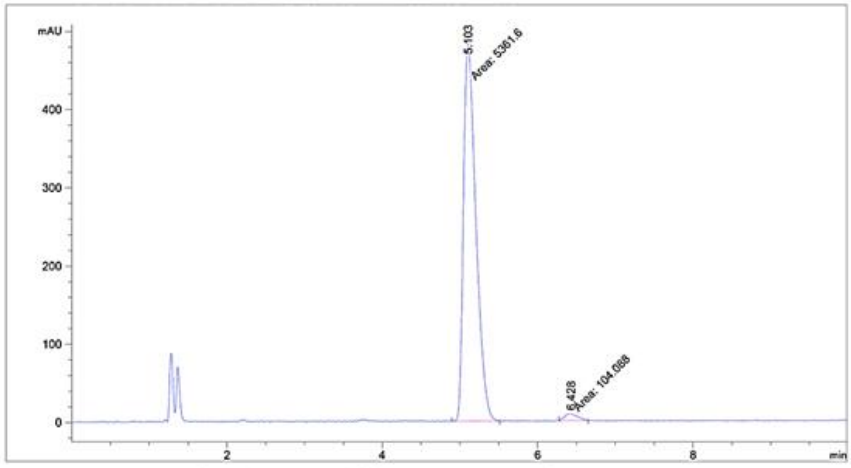
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.416	MM	0.2027	903.84863	74.31981	45.0255
2	11.665	MM	0.2268	1103.56628	81.11297	54.9745



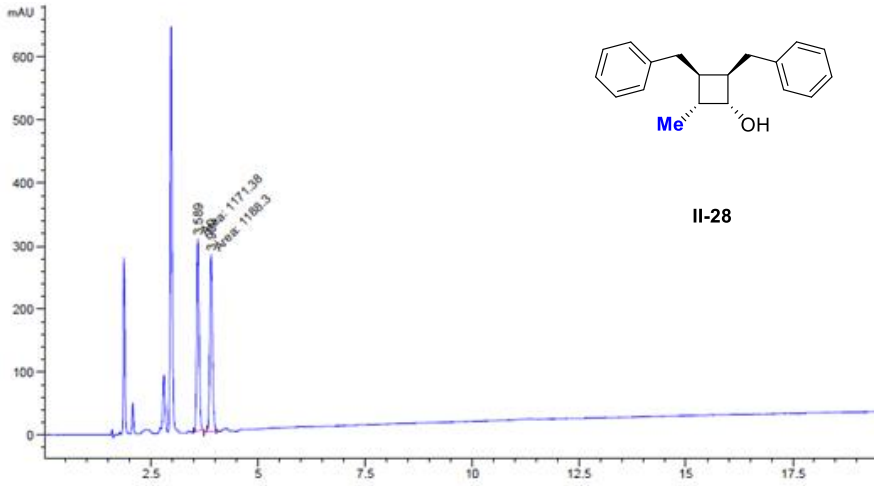
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.025	MM	0.2088	46.70849	3.72920	3.0720
2	11.115	MM	0.2390	1473.74756	102.79061	96.9280



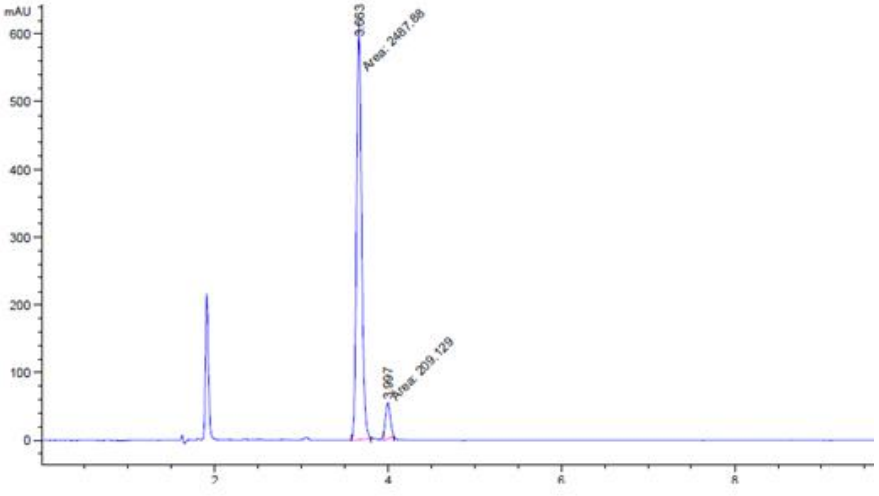
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.203	MM	0.1879	775.68658	68.79118	50.7194
2	6.487	MM	0.2384	753.68103	52.68371	49.2806



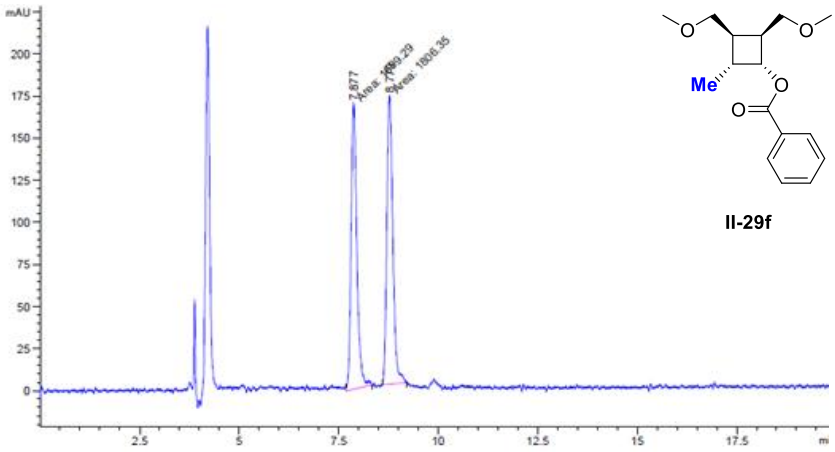
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.103	MM	0.1851	5361.60449	482.70752	98.0956
2	6.428	MM	0.1960	104.08816	8.85208	1.9044



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.589	MM	0.0638	1171.38452	305.87967	49.6415
2	3.900	MM	0.0702	1188.30347	282.20023	50.3585

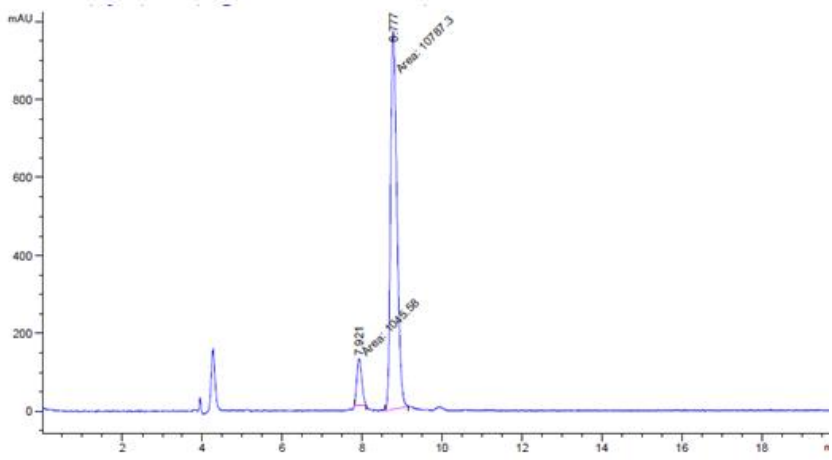


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.663	MM T	0.0677	2487.88135	612.77393	92.2459
2	3.997	MM T	0.0657	209.12927	53.07629	7.7541

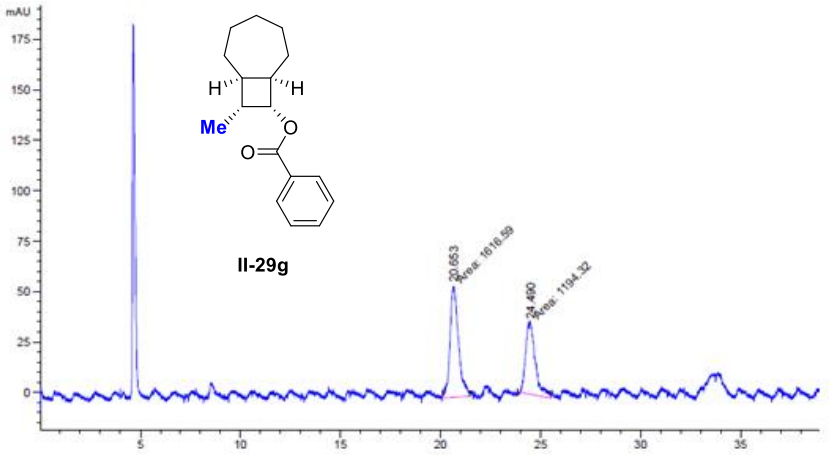


II-29f

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.877	MP	0.1669	1699.29126	169.69431	48.4731
2	8.779	PP	0.1758	1806.34802	171.26292	51.5269

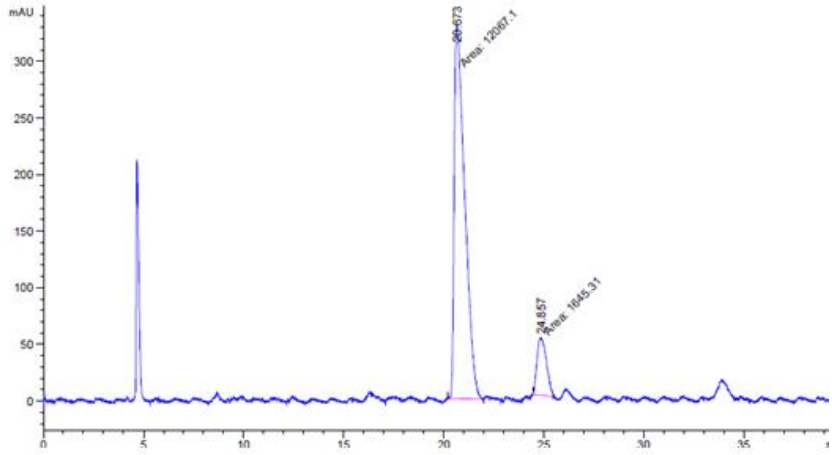


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.921	MM T	0.1434	1045.58398	121.55928	8.8363
2	8.777	MM T	0.2122	1.07873e4	970.06317	91.1637



II-29g

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	20.653	MM T	0.5000	1616.59058	55.30363	57.5113
2	24.490	MM T	0.5542	1194.31836	35.91872	42.4887



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	20.673	MM T	0.6093	1.20671e4	330.06625	88.0013
2	24.857	MM T	0.5385	1645.30762	50.92670	11.9987

Chapter 3

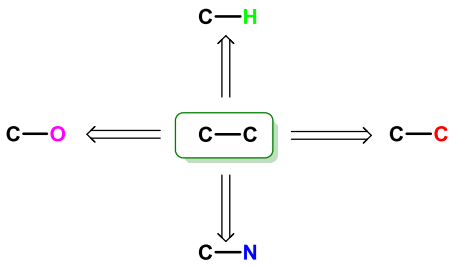
STEREOSPECIFIC COPPER-CATALYZED SUBSTITUTION REACTION OF PROPARGYLIC AMMONIUM SALTS.

3. STEREOSPECIFIC COPPER-CATALYZED SUBSTITUTION REACTION OF PROPARGYLIC AMMONIUM SALTS.

3.1. Background.

3.1.1. Transition-Metal Catalyzed Reaction of Nitrogen-Containing Molecules.

In the last decades, transition-metal catalyzed reactions have emerged as one of the most powerful strategies for the formation of carbon-carbon bonds.[1] Much recently, powerful efforts have been made through the discovery of more stable and easily available electrophiles for cross-coupling reactions (**Scheme *3-1***).



Scheme 3-1: New electrophiles in cross-coupling reaction.

[1] a) Beller, M.; Bolm, C. *Transition Metals for Organic Synthesis: Building Blocks and Fine Chemicals.* WILEY-VCH Verlag GmbH; Weinheim, 1998. b) Bates, R. *Organic Synthesis Using Transition Metals, Second Edition.* John Wiley & Sons, Ltd; Weinheim, 2012. c) Colacot, T. *New Trends in Cross-Coupling: Theory and Applications.* Royal Society of Chemistry, 2015. d) Johansson-Seechurn, C. C. C.; Kitching, M. O.; Colacot, T. J.; Snieckus, V. *Angew. Chem. Int. Ed.* **2012**, *51*, 5062-5085. e) Cherney, A. H.; Kadunce, N. T.; Reisman, S. E. *Chem. Rev.* **2015**, *115*, 9587-9652.

Several approaches for the activation of C-H,[2] C-O[3] and C-C[4] bonds have been developed through the last years. These advances have provided to the organic chemistry community with a completely new toolbox for making new molecules and design new synthetic strategies.

However, reaction involving transition-metal C-N cleavage is far less explored.[5] This is not surprising, taking account of the high dissociation energy of the C-N bond (356 KJ/mol).[6]

Nevertheless, the high number of nitrogen-containing molecules in pharmaceuticals and natural products, makes strategies to activate C-N bonds extremely desirable for the synthesis community, because late stage functionalization of molecules is key to the discovery of new leads in the early drug discovery stage.[7] In addition, strategies aiming for the activation of C-N bonds, would benefit of the large variety of methods to prepare amine-containing molecules.[8]

[2] a) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 624-655. b) Wencel-Delord, J.; Dröge, T.; Liu, F.; Glorius, F. *Chem. Soc. Rev.* **2011**, *40*, 4740-4761. c) Yang, L.; Huang, H. *Chem. Rev.* **2015**, *115*, 3468-3517. d) He, J.; Wasa, M.; Chan, K. S. L.; Shao, Q.; Yu, J. Q. *Chem. Rev.* **2017**, *117*, 8754-8786. e) Yang, Y.; Lan, J.; You, J. *Chem. Rev.* **2017**, *117*, 8787-8863. f) Wei, Y.; Hu, P.; Zhang, M.; Su, W. *Chem. Rev.* **2017**, *117*, 8864-8907.

[3] Quasdorf, K. W.; Tian, X.; Garg, N. K. *J. Am. Chem. Soc.* **2008**, *130*, 14422-14423. b) Li, W. N.; Wang, Z. L. *RSC Adv.* **2013**, *3*, 25565-25575. c) Cornella, J.; Zarate, C.; Martin, R. *Chem. Soc. Rev.* **2014**, *43*, 8081-8097. d) Tobisu, M.; Chatani, N. *Acc. Chem. Res.* **2015**, *48*, 1717-1726. e) Tollefson, E. J.; Hanna, L. E.; Jarvo, E. R. *Acc. Chem. Res.* **2015**, *48*, 2344-2353. f) Su, B.; Cao, Z. C.; Shi, Z. J. *Acc. Chem. Res.* **2015**, *48*, 886-896.

[4] a) Jun, C. H. *Chem. Soc. Rev.* **2004**, *33*, 610-618. b) Park, Y. J.; Park, J. W.; Jun, C. H. *Acc. Chem. Res.* **2008**, *41*, 222-234. c) Xia, Y.; Lu, G.; Liu, P.; Dong, G. *Nature* **2016**, *539*, 546-550.

[5] a) Ouyang, K.; Hao, W.; Zhang, W. X.; Xi, Z. *Chem. Rev.* **2015**, *115*, 12045-12090. b) Wang, Q.; Su, Y.; Li, L.; Huang, H. *Chem. Soc. Rev.* **2016**, *45*, 1257-1272.

[6] Luo, Y. R. *Comprehensive Handbook of Chemical Bond Energies*, CRC Press, Boca Raton, FL, 2007.

[7] a) Vitaku, E.; Smith, D. T.; Njardarson, J. T. *J. Med. Chem.* **2014**, 57, 10257-10274. b) Blakemore, D. C.; Castro, L.; Churcher, I.; Rees, D. C.; Thomas, A. W.; Wilson, D. M.; Wood, A. *Nat. Chem.* **2018**, *10*, 383-394.

[8] a) Nugent, T. C. *Chiral Amine Synthesis;* Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, 2010. b) Ruiz-Castillo, P.; Buchwald, S. L. *Chem. Rev.* **2016**, *116*, 12564-12649.

However, a comprehensive review of the literature regarding C-N activation exceeds the scope of the introduction in this chapter. Therefore, only literature concerning ammonium salts will be included in the next sections.

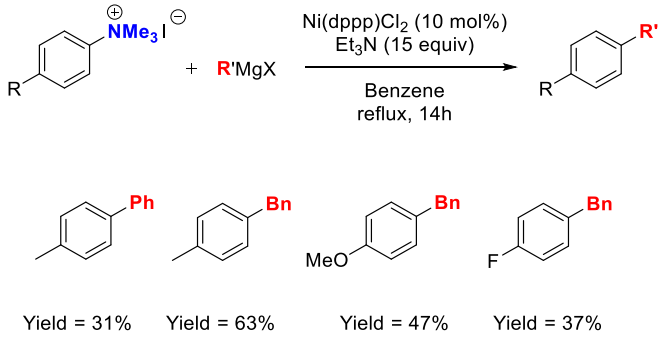
3.1.2. Cross-Coupling Reactions of Ammonium Salts.

As we have mentioned earlier in this chapter, C-N bonds possess a high dissociation energy. An interesting way to bypass this problem is to convert the corresponding amine into an ammonium salt. This functional group is easily prepared from amines and the dissociation energy of the C-N bond drop significantly. In this section, different methodologies to activate C-N bond using ammonium salts will be explained.

3.1.2.1. Arylic Ammonium salts.

In a pioneering work, Wenkert and co-workers, succeeded in the development of the first metal-catalyzed cross-coupling of arylic ammonium salts as electrophiles. They envisioned a Kumada-type cross-coupling using Grignard reagents as nucleophiles in the presence of a nickel catalyst (**Scheme *3*-*2***).[9] The best results were obtained using alkyl Grignard reagents, but the use of arylic compounds was also compatible. Although the results were not excellent, this seminal publication served as inspiration to other groups.

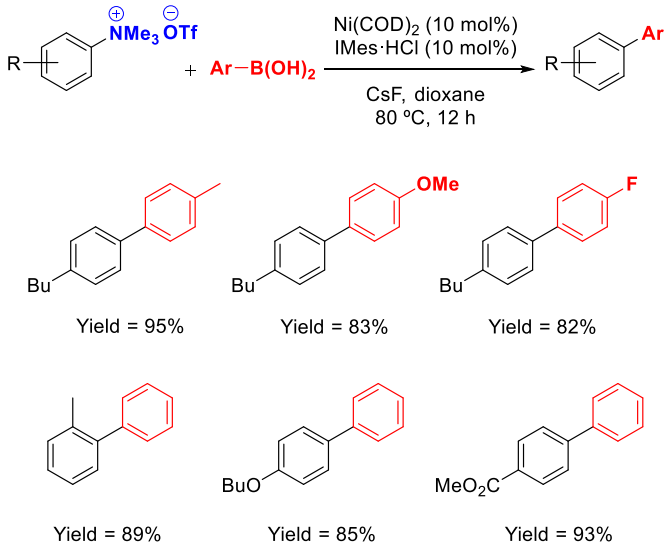
[9] Wenkert, E.; Han, A. -L.; Jenny, C. -J. *J. Chem. Soc., Chem. Commun.* **1988**, 975-976.



Scheme 3-2: Kumada-type cross-coupling of ammonium salts with Grignard reagents.

It was not until 2003, that Macmillan and co-workers, discovered that aryltrimethylammonium salts could be used as partners in Suzuki cross-coupling reactions with aryl boronic acids, using a Ni(0) catalyst and a bulky ligand (**Scheme *3-3***).[10] MacMillan was also the first that introduced triflate as a critical counteranion in these reactions. The scope of the transformation was fairly broad, both the anilinium and the boronic acid, obtaining excellent yields in all reported examples.

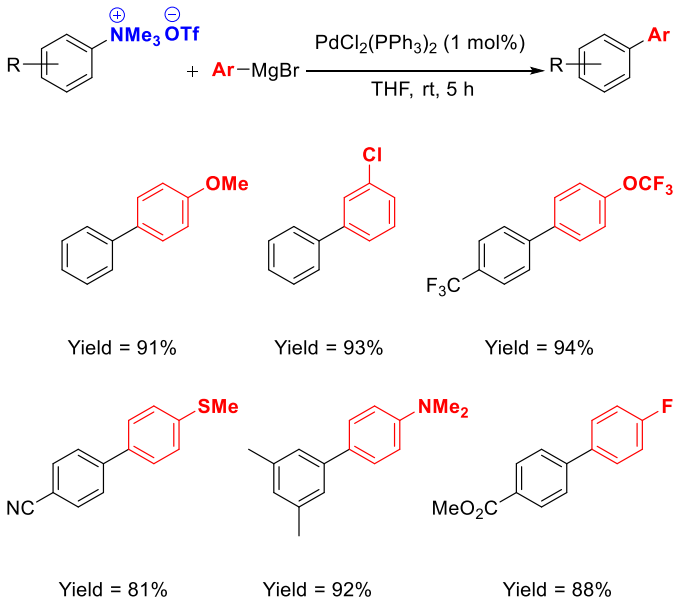
[10] Blakey, S. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2003**, *125*, 6046-6047.



Scheme 3-3: First Suzuki cross-coupling of ammonium salts with aryl boronic acids.

In 2010, Reeves and co-workers discovered a palladium-catalyzed Kumada cross-coupling of aryl trimethylammonium salts with Grignard reagents (**Scheme *3-4***).[11] Using triflate as counteranion and a commercially available palladium complex, they obtained excellent results, improving those obtained previously by Wenkert.[9]

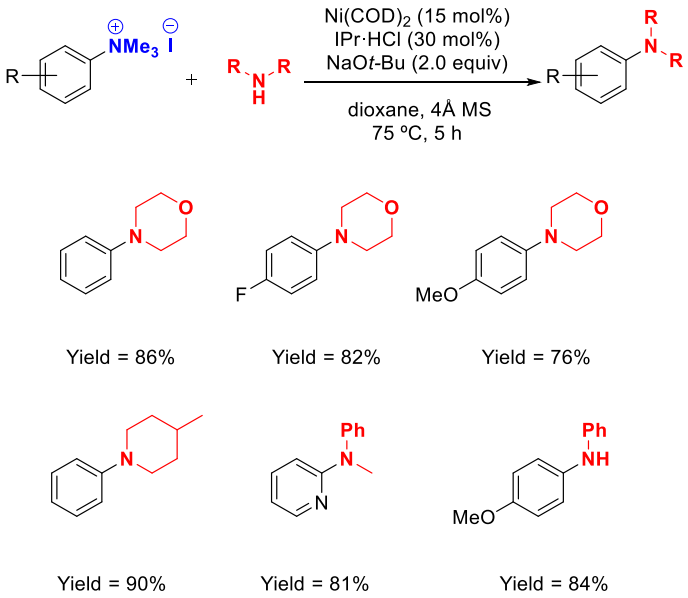
[11] Reeves, J. T.; Fandrick, D. R.; Tan, Z.; Song, J. J.; Lee, H.; Yee, N. -K.; Senanayake, C. H. *Org. Lett.* **2010**, *12*, 4388-4391.



Scheme 3-4: Kumada-type palladium catalyzed cross-coupling of aryltrimethylammonium salts.

In 2014, Wang and co-workers reported the Buchwald-Hartwig type cross-coupling reaction between aryl ammonium salts and simple amines (**Scheme *3-5***).[12] As catalyst, they used the commercially available $Ni(COD)_2$ and a *N*-heterocyclic carbene turned out to be the best ligand for the transformation. Both primary and secondary amine worked well with the reaction conditions. They succeeded in the one-pot amino group exchange of a dimethylamine into a morpholine moiety.

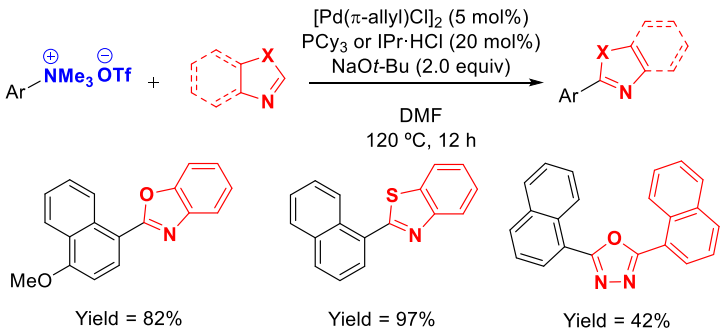
[12] Zhang, X. -Q.; Wang, Z. -X. *Org. Biomol. Chem.*, **2014**, *12*, 1448-1453.



Scheme 3-5: Nickel catalyzed cross-coupling between aryltrimethylammonium salts and amines.

The same group, in 2015, published the C-H arylation of various heterocycles catalyzed by palladium, using aryl trimethylammonium salts as electrophiles (**Scheme *3-6***).[13] Both (benzo)oxazoles and (benzo)thiazoles worked well in the reaction conditions, obtaining moderate to excellent yields. They proposed a catalytic cycle where the key step was the C-H palladation in the presence of NaO*t*-Bu.

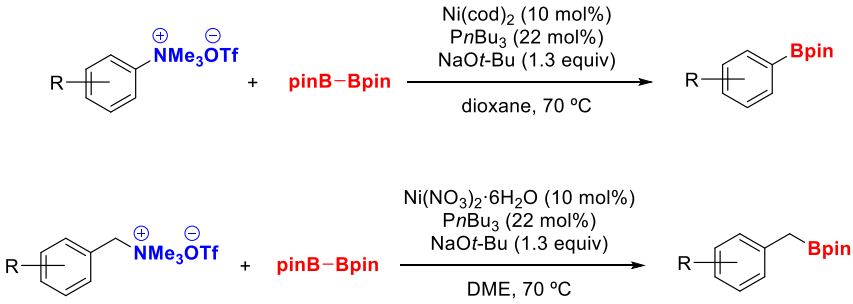
[13] Zhu, F.; Tao, J. -L.; Wang, Z. -X. *Org. Lett.* **2015**, *17*, 4926-4929.



Scheme 3-6: Palladium catalyzed C-H arylation of heterocycles.

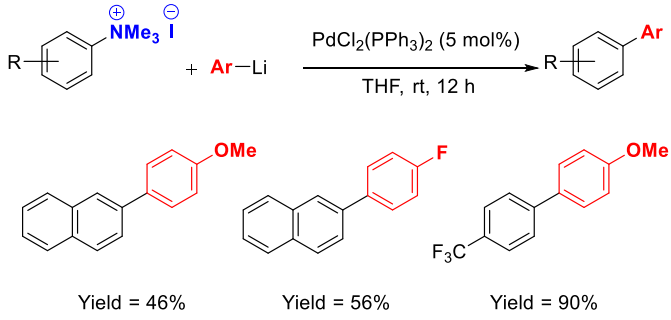
Itami and co-workers realized that there were a wide repertoire of functionalization methods using dimethylamine as directing group. However, the methodologies to transform this group were still scarce. They envisioned the transformation of the dimethylamino group into trimethylammonium salts to make a C-N nickel-catalyzed borylation and later take advantage of the wide amount of C-B functionalization methods (**Scheme *3-7***). Both aryl and benzyl ammonium salts were suitable for the borylation and they succeeded with the transformation of the C-B bond.[14] Simultaneously, Shi and co-workers reported the same transformation.[15]

[14] Zhang, H.; Hagihara, S.; Itami, K. *Chem. Eur. J.* **2015**, *21*, 16796-16800.
[15] Hu, J.; Sun, H.; Cai, W.; Pu, X.; Zhang, Y.; Shi, Z. *J. Org. Chem.* **2016**, *81*, 14-24.



Scheme 3-7: Nickel-catalyzed borylation of ammonium salts.

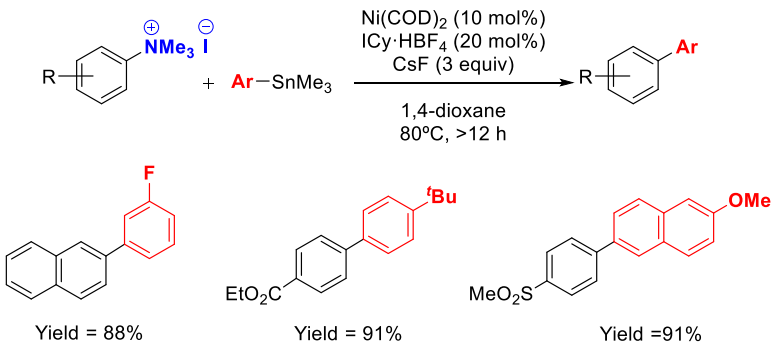
In 2016, Wang, Uchiyama and co-workers, reported a methodology for the cross-coupling of aryl ammonium salts with organolithium reagents (**Scheme *3-8***). Their conclusion included that the best catalytic system for this transformation was the commercially available $PdCl_2(PPh_3)_2$ and that the counteranion played a key role in the transformation. In this case, iodine was superior to other counteranion such as triflate or tetrafluoroborate.[16]



Scheme 3-8: Cross-coupling of aryl trimethylammonium salts and organolithium reagents catalyzed by palladium.

[16] Yang, Z. K.; Wang, D. -Y.; Minami, H.; Ogawa, H.; Ozaki, T.; Saito, T.; Miyamoto, K.; Wang, C.; Uchiyama, M. *Chem. Eur. J.* **2016**, *22*, 15693-15699.

The same group published a methodology for the Stille cross-coupling of aryl ammonium salts catalyzed by nickel (**Scheme *3-9***).[17] This was the first Stille coupling using this kind of electrophiles, which opened the door to further investigations. The functional group tolerance was very high and the mechanism they proposed was the typical for a Stille coupling, although some interesting conclusion could be obtained from their mechanism experiments. Despite of CsF seemed to act only as a base to free the ICy ligand, and allowed the oxidative addition step, it was crucial in the transmetalation. DFT calculations showed that the barrier was lowered by a substantial amount if fluorine anions were attached to the metal centre during the reaction.

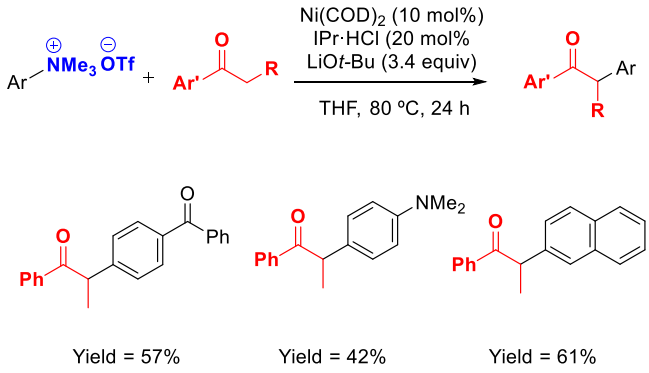


Scheme 3-9: Stille Cross-coupling of aryl ammonium salts.

Wang and co-workers published in 2016, a method for the α-arylation of ketones, taking advantage of the unique reactivity of aryl ammonium salts (**Scheme *3-10***).[18] The choice of catalyst was nickel and after a large

[17] Wang, D. Y.; Kawahata, M.; Yang, Z. K.; Miyamoto, K.; Komagawa, S.; Yamaguchi, K.; Wang, C.; Uchiyama, M. *Nat. Commun.* **2016**, *7*, 12937-12945.
[18] Li, J.; Wang, Z. X. *Org. Biomol. Chem.* **2016**, *14*, 7579-7584.

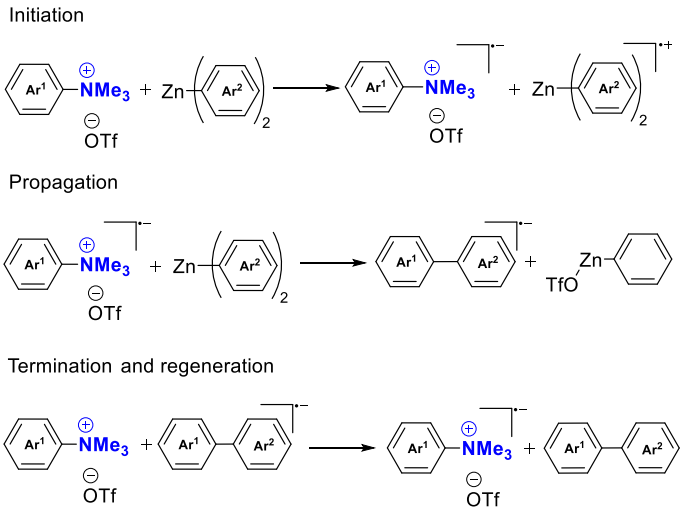
screening of ligands and bases they found that IPr·HCl and LiO*t*-Bu excelled in this reaction.



Scheme 3-10: Nickel catalyzed α-arylation of ketones.

In 2017, Wang, Uchiyama and co-workers, reported a very interesting procedure for the transition metal-free cross-coupling of aryltrimethylammonium triflates with diarylzinc compounds. The most interesting fact in this work was the proposed mechanism. They proposed that aryl ammonium compounds could suffer a SET process generating the corresponding radical anion. This radical anion propagated with another molecule of diarylzinc, forming another radical anion, which in the final step reacted with another aryl ammonium molecule to generate the desired product and restarted the catalytic cycle (**Scheme *3-11***).[19]

[19] Wang, D. Y.; Morimoto, K.; Yang, Z. -K.; Wang, C.; Uchiyama, M. *Chem. Asian. J.* **2017**, *12*, 2554-2557.

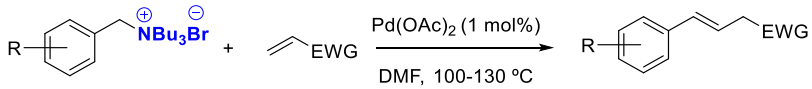


Scheme 3-11: Mechanism for the metal-free cross-coupling of aryltrimethylammonium salts.

3.1.2.2. Benzylic Ammonium salts.

In 1995, Zhuangyu succeeded in perform the very first metal catalyzed cross-coupling of benzylic ammonium salts. The vinylation of the substrates took place in the presence of low amounts of palladium(II) acetate with moderate yields. Mechanistic experiments showed evidences of a radical mechanism (**Scheme *3-12***).[20] They proposed that the radical is formed by reductive cleavage of the quaternary ammonium salt in the presence of palladium(0).

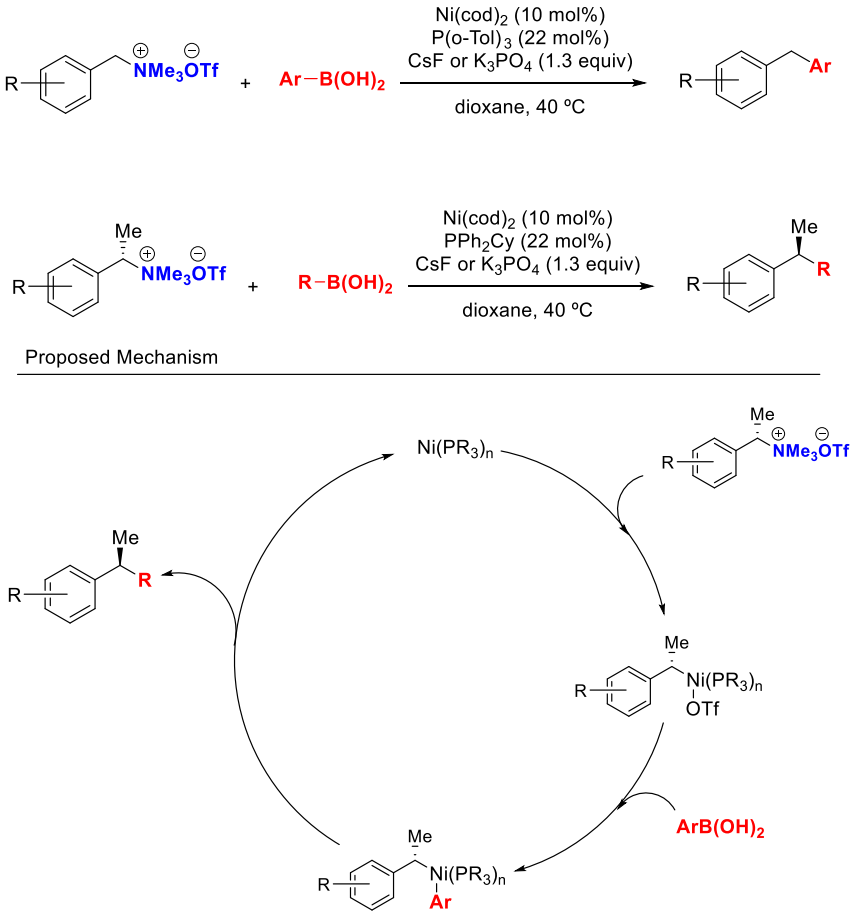
[20] Yi, P.; Zhuangyu, Z.; Hongwen, H. *Synthesis* **1995**, *3*, 245-247.



Scheme 3-12: Vinylation of benzylic ammonium salts catalyzed by palladium.

In an inspiring work, Watson and co-workers reported the stereospecific nickel-catalyzed Suzuki cross-coupling between benzylic trimethylammonium salts and boronic acids (**Scheme *3-13***).[21] Both primary and secondary benzylic compounds could be used, and they obtained high levels of stereospecificity starting from enriched benzylic ammonium salts. This publication represents the first stereospecific cross-coupling reaction using a secondary ammonium salt as electrophile. Also, the importance of the triflate as counteranion is highlighted. They proposed that the reaction started with the oxidative addition of the electron rich Ni(0) complex into the C-N bond. Transmetalation with the boronic acid and then reductive elimination produce the desired product. A year later, they reported the same transformation with improved reaction conditions. They bypass the need of a ligand in the cross-coupling reaction and they only used $Ni(COD)_2$ as catalyst.[22] Also in 2016, they reported the stereospecific borylation of benzylic ammonium salts catalyzed by nickel with excellent results.[23] Itami and coworkers also reported a similar borylation.[14]

[21] Maity, P.; Shacklady-McAtee, D. M.; Yap, G. P. A.; Sirianni, E. R.; Watson, M. P. *J. Am. Chem. Soc.* **2013**, *135*, 280-285.
[22] Shacklady-McAtee, D. M.; Roberts, K. M.; Basch, C. H.; Song, Y. G.; Watson, M. P. *Tetrahedron* **2014**, *70*, 4257-4263.
[23] Basch, C. H.; Cobb, K. M.; Watson, M. P. *Org. Lett.* **2016**, *18*, 136-139.

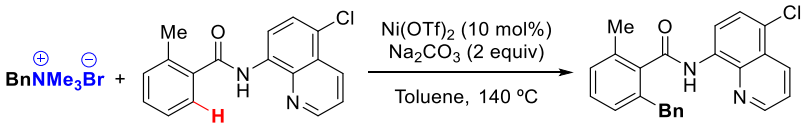


Scheme 3-13: Cross-coupling of benzylic ammonium salts catalyzed by nickel.

After Watson, there have been several reports on the Suzuki cross-coupling of benzylic ammonium salts. In 2017, the group of Tu, published the Suzuki cross-coupling between benzylic ammonium salts with aryl boronic acids using a *N*-heterocyclic carbene nickel pincer complexes as

catalyst and the groups of Zhao and Phipps reported the same transformation using palladium.[24]

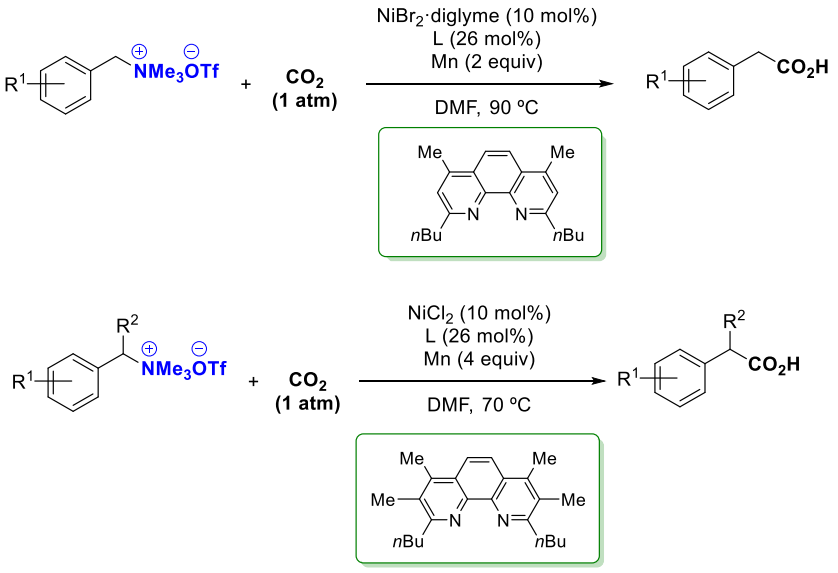
The groups of Chatani and Wei, published the C-H activation of aromatic amides with benzylic ammonium salts catalyzed by nickel (**Scheme *3-14***).[25]



Scheme 3-14: Nickel-catalyzed benzylation of aromatic amides.

In 2016, Martin and co-workers reported the formal cross-electrophile coupling between benzylic ammonium salts and carbon dioxide, leading to α-substituted phenylacetic acids (**Scheme *3-15***).[26] They used commercially available nickel salts, along with phenanthroline type ligands to obtain the desired products with good results. They also completely avoided the common problems of cross-electrophile reactions, such as homodimerization and β-hydride elimination.

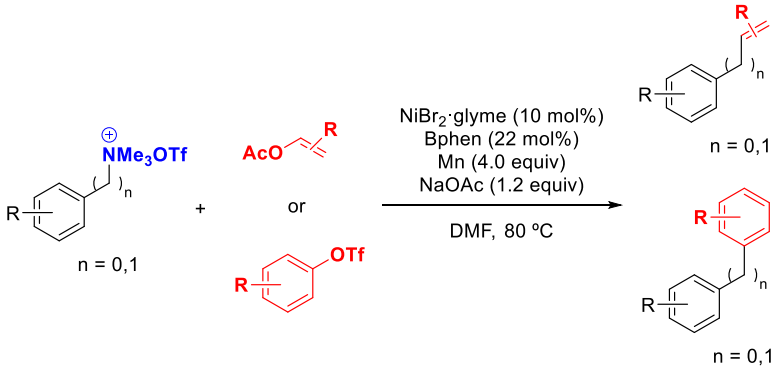
[24] a) Liu, X. Y.; Zhu, H. B.; Shen, Y. J.; Jiang, J.; Tu, T. *Chinese Chemical Letters* **2017**, *28*, 350-353. b) Wang, T.; Yang, S.; Xu, S.; Han, C.; Guo, G.; Zhao, J. *RSC Adv.* **2017**, *7*, 15805-15808. c) Türtscher, P. L.; Davis, H. J.; Phipps, R. J. *Synthesis* **2018**, *50*, 793–802.
[25] a) Sasagawa, A.; Yamaguchi, M.; Ano, Y.; Chatani, N. *Isr. J. Chem.* **2017**, *57*, 964-967. b) Li, J.; Zheng, Z.; Xiao, T.; Xu, P.F.; Wei, H. *Asian J. Org. Chem.* **2018**, *7*, 133-136.
[26] Moragas, T.; Gaydou, M.; Martin, R. *Angew. Chem. Int. Ed.* **2016**, *55*, 5053-5057.



Scheme 3-15: Carboxylation of benzylic ammonium salts catalyzed by nickel.

In 2019, Shu and coworkers have reported a procedure for the nickel-catalyzed cross-electrophile reaction between benzyl or aryltrimethylammonium salts and C-O electrophiles.[27] In this way, the ammonium salts could be coupled either with a range of vinyl acetates or aryl triflates. Mechanistic experiments suggest a radical mechanism (**Scheme *3-16***).

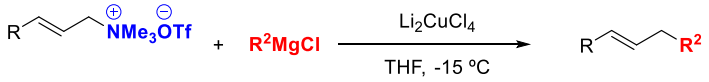
[27] He, R. D.; Li, C. L.; Pan, Q. Q.; Guo, P.; Liu, X. Y; Shu, X. Z. *J. Am. Chem. Soc.* **2019**, *141*, 12481-12486.



Scheme 3-16: Nickel-catalyzed cross-electrophile reaction of trimethylammonium salts.

3.1.2.3. Allylic Ammonium Salts.

In 1980, Langlois and Dressaire reported the allylic substitution of ammonium salts with Grignard reagents in the presence of dilithium dichlorocuprate (**Scheme *3-17***).[28] In 1987, the groups of Hosomi and Gupton published the same transformation.[29] In 1982, Hirao and coworkers reported the Pd-catalyzed Tsuji-Trost reaction of allylic ammonium salts with carbon nucleophiles. In most cases, they obtained almost no regioselectivity.[30]



Scheme 3-17: Allylic substitution of ammonium salts.

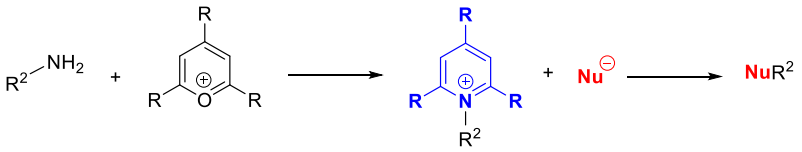
[28] Dressaire, G.; Langlois, Y. *Tetrahedron Lett.* **1980**, *21*, 67-70.

[29] a) Hosomi, A.; Hoashi, K.; Tominaga, Y. *J. Org. Chem.* **1987**, *52*, 2947-2948. b) Gupton, J. T.; Layman, W. J. *J. Org. Chem.* **1987**, *52*, 3683-3686.

[30] Hirao, T.; Yamada, N.; Oshiro, Y.; Agawa, T. *J. Organomet. Chem.* **1982**, *236*, 409-411.

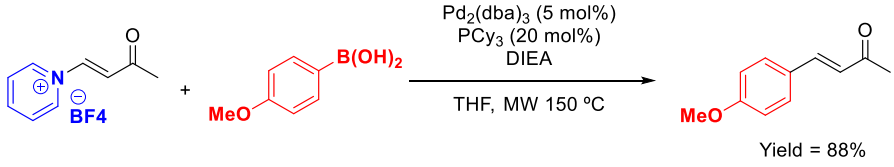
3.1.2.4. Pyridinium Salts.

It was Katritzky and co-workers in 1976 who discovered the potential of pyridinium salts as leaving groups.[31] It was an easy way to transform amines into good leaving groups (**Scheme *3-18***).



Scheme 3-18: Pyridinium salts as leaving group.

However, it was not until 2007 when Buszek and Brown reported the use of pyridinium salts as partners in cross-coupling reaction. They reported the palladium-catalyzed Suzuki cross-coupling reaction of *N*-vinylpyridinium and ammonium tetrafluoroborate salts with boronic acids (**Scheme *3-19***).[32]



Scheme 3-19: Suzuki cross-coupling of vinylpyridinium salts.

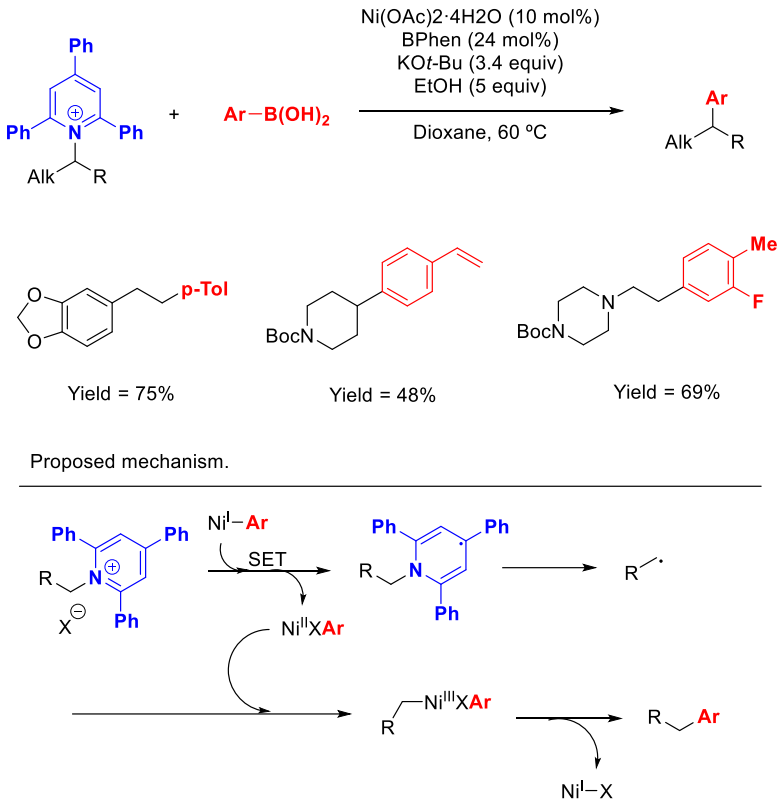
[31] a) Bapat, J. B.; Blade, R. J.; Boulton, A. J.; Espztajn, J.; Katritzky, A. R.; Lewis, J.; Molina-Buendia, P.; Nie, P. L.; Ramsden, C. A. *Tetrahedron Lett.* **1976**, *31*, 2691-2694. b) Katritzky, A. R.; Marson, C. M. *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 420-429. c) Katritzky, A. R.; Brycki, B. *Can. J. Chem.* **1986**, *64*, 1161-1169.

[32] Buszek, K. R.; Brown, N. *Org. Lett.* **2007**, *9*, 707-710.

In 2016, Watson and co-workers reported the sp^3-sp^2 Suzuki cross-coupling of alkylpyridinium salts with boronic acids (**Scheme *3-20***).[33] With this strategy, normal alkylamines could be used as alkylating agents, being the first example of this kind of transformation. They proposed a radical mechanism based on mechanistic experiments. The pyridinium underwent a SET process with a Ni(I) complex to produce an alkyl radical and a Ni(II) complex. Both molecules reacted to form a Ni(III) complex which after reductive elimination produce the desired product and regenerate the Ni(I) complex. The same group extended this methodology to benzylic amines for the synthesis of diarylmethanes.[34]

[33] Basch, C. H.; Liao, J.; Xu, J.; Piane, J. J.; Watson, M. P. *J. Am. Chem. Soc.* **2017**, *139*, 5313-5316.

[34] a) Liao, J.; Guan, W.; Boscoe, B. P.; Tucker, J. W.; Tomlin, J. W.; Garnsey, M. R.; Watson, M. P. *Org. Lett*. **2018**, *20*, 3030-3033. b) Guan, W.; Liao, J.; Watson, M. P. *Synthesis* **2018**, *50*, 3231-3237.

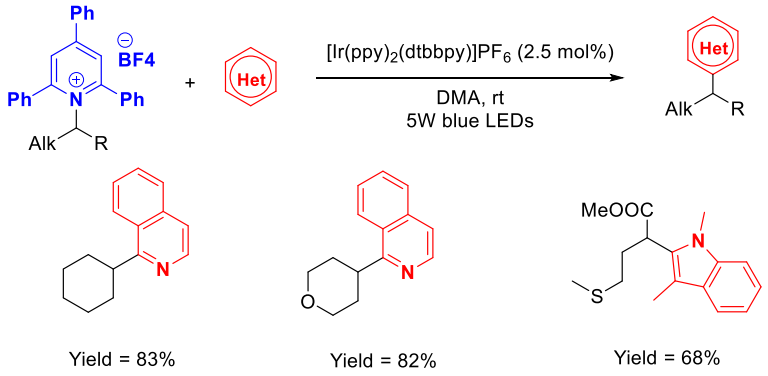


Scheme 3-20: Nickel-catalyzed cross-coupling of alkylammonium salts.

In the same year, Glorius and co-workers, reported a photocatalytic strategy to carry out a similar transformation. Using an iridium photocatalyst, under visible-light conditions, they performed the cross-coupling between alkylpyridinium salts and a variety of heterocycles (**Scheme *3-21***).[35] They also could use protected amino acids as starting

[35] Klauck, F. J. R.; James, M. J.; Glorius, F. *Angew. Chem. Int. Ed.* **2017**, *56*, 12336-12339.

materials with excellent results. They proposed a SET process to produce a radical from the alkylpyridinium salt. Recently, Watson and coworkers have reported a nickel-catalyzed Suzuki cross-coupling between alkylpyridinium salts from aminoacids and boronic acids or boroxines.[36]



Scheme 3-21: Visible-light mediated cross-coupling of alkylammonium salts.

Glorius and coworkers have reported this year a procedure for the dicarbofuntionalization of styrenes using benzylic radicals from benzylpyridinium salts.[37]

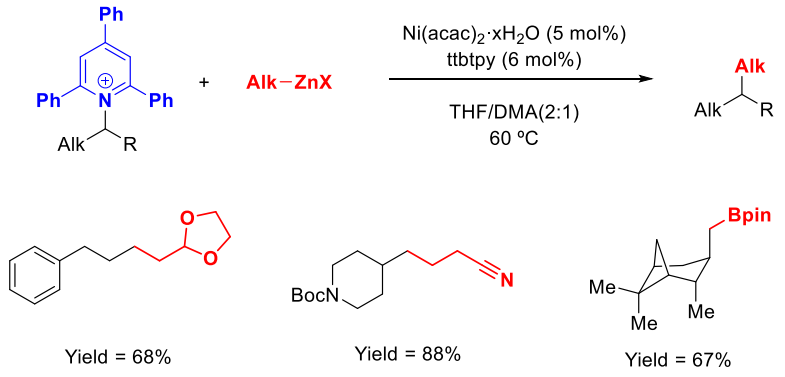
Also in 2019, Watson and co-workers have reported the alkyl-alkyl cross-coupling of pyridinium salts with alkylzinc reagents catalyzed by nickel (**Scheme *3-22***).[38] This is the very first sp^3-sp^3 bond formation using alkyl amine derivatives with inactivated alkyl groups. It worked for both

[36] Hoerner, M. E.; Baker, K. M.; Basch, C. H.; Bampo, E. M.; Watson, M. P. ASAP. DOI: 10.1021/acs.orglett.9b02643

[37] Klauck, F. J. R.; Yoon, H.; James, M. J.; Lautens, M.; Glorious, F. *ACS Catal.* **2019**, *9*, 236-241.

[38] Plunkett, S.; Basch, C. H.; Santana, S. O.; Watson, M. P. *J. Am. Chem. Soc.* **2019**, *141*, 2257-2262.

primary and secondary amines and presented very good functional group tolerance.

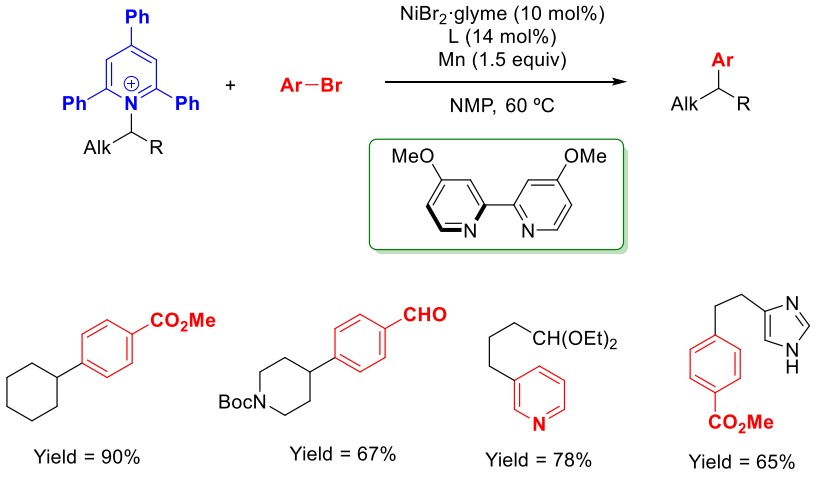


Scheme 3-22: Alkyl-alkyl Negishi cross-coupling of pyridinium salts.

Recently, Martin and co-workers have reported the reductive deaminative arylation of alkylpyridinium salts with aromatic halides catalyzed by nickel (**Scheme *3-23***).[39] Mechanistic experiments suggested that nickel is not involved into the C-N cleavage. Watson, Molander and Rueping have reported similar transformation.[40]

[39] Martin-Montero, R.; Yatham, V. R.; Yin, H.; Davies, J.; Martin, R. *Org. Lett.* **2019**, *21*, 2947-2951.

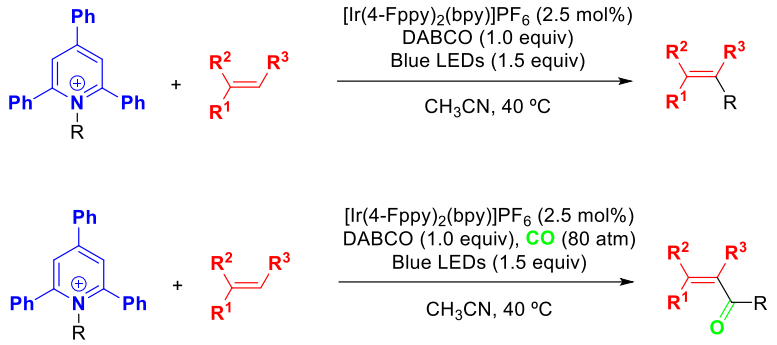
[40] a) Yi, J.; Badir, S. O.; Kammer, L. M.; Ribagorda, M.; Molander, G. A. *Org. Lett.* **2019**, *21*, 3346-3351. b) Liao, J.; Basch, C. H.; Hoerner, M. E.; Talley, M. R.; Boscoe, B. P.; Tucker, J. W.; Garnsey, M. R.; Watson, M. P. *Org. Lett*. **2019**, *21*, 2941-2946. c) Yue, H.; Zhu, C.; Shen, L.; Geng, Q.; Hock, K. J.; Yuan, T.; Cavallo, L.; Rueping, M. *Chem. Sci*. **2019**, *10*, 4430-4435.



Scheme 3-23: Reductive deaminative arylation catalyzed by nickel.

Recently, Xiao, Lu and coworkers have reported an alkyl-heck reaction using alkylpyridinium salts as electrophiles via a radical mechanism.[41] The reaction is catalyzed by iridium and they were able to perform also the carbonylative heck reaction adding CO (80 atm) to the reaction mixture.

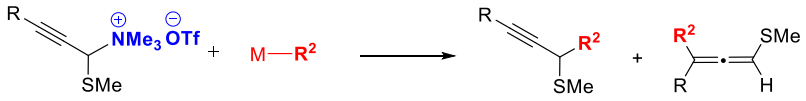
[41] Jiang, X.; Zhang, M. M.; Xiong, W.; Lu, L. Q.; Xiao, W. J. *Angew. Chem. Int. Ed.* **2019**, *58*, 2402-2406.



Scheme 3-24: Iridium catalyzed Heck-type reaction using alkylpyridinium salts as electrophiles.

3.1.2.5. Propargylic ammonium salts.

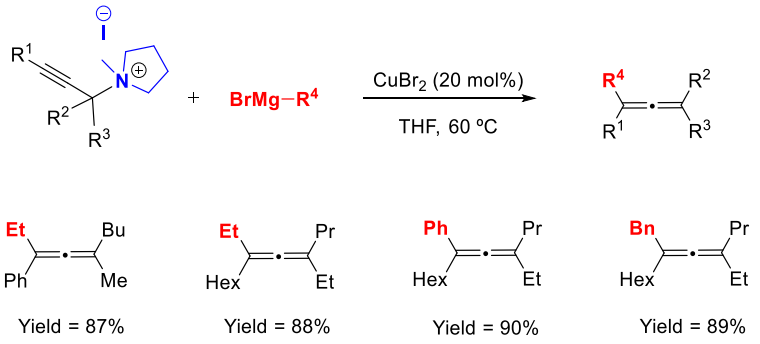
When we started the project presented in this chapter, there was only one example of propargylic ammonium salts used as electrophiles. In 2007, Murai and co-workers, reported the reaction between 1-methylthiopropargylammonium salts with a variety of organometallic reagents (**Scheme *3-25***).[42] When they used aryl Grignard reagents, they obtained a mixture of propargyl sulfides or allenyl sulfides, being the mayor product the first one. However, when they used organocopper reagents they obtained allenyl sulfides as single regioisomer. Finally, when they used an organolithium reagent, the salts undergo dimerization.



Scheme 3-25: Substitution reaction of 1-methylthiopropargyl ammonium salts.

[42] Murai, T.; Fukushima, K.; Mutoh, Y. *Org. Lett.* **2007**, *9*, 5295-5298.

During the development of the work presented in this chapter, Ma and co-workers reported the synthesis of tetrasubstituted allenes using propargylic ammonium salts as starting materials (**Scheme *3-26***).[43] They used copper(II) bromide as catalyst and the propose an S_N2' pathway for the reaction. The sterospecificity of the transformation was not studied.



Scheme 3-26: Copper-catalyzed allene synthesis from propargylic ammonium salts.

3.1.3. Cross-Coupling of Propargylic compounds.

The catalytic propargylic substitution reaction is a powerful method to synthetize new chiral propargylic compounds. In addition, the alkyne moiety is an extremely versatile functional group.[44] Furthermore, there are a wide number of natural products, pharmaceuticals and fine chemicals containing propargylic moieties in their structure (**Figure *3-1***).[45]

[43] Ma, S.; Liu, Q.; Tang, X.; Cai, Y. *Asian J. Org. Chem*. **2017**, *6*, 1209-1212.

[44] a) Diederich, F., Stang, P. J., Tykwinski, R. R. *Acetylene Chemistry*, Wiley-VCH: New York, 2005. b) *The Chemistry of Triple-Bonded Functional Groups*. Patai, S. Wiley: New York, 1994.

[45] a) Konishi, M.; Ohkuma, H.; Matsumoto, K.; Tsuno, T.; Kamei, H.; Miyaki, T.; Oki, T.; Kawaguchi, H.; Van Duyne, G. D.; Clardy, J. *J. Antibiot.* **1989**, *42*, 1449-1452. b) Thompson, A. S.; Corley, E. G.; Huntington, M. F.; Grabowski, E. J. J. *Tetrahedron Lett.* **1995**, *36*, 8937-8940. c) Wright, J. L.; Gregory, T. F.; Kesten, S. P.; Boxer, P. A.; Serpa, K.

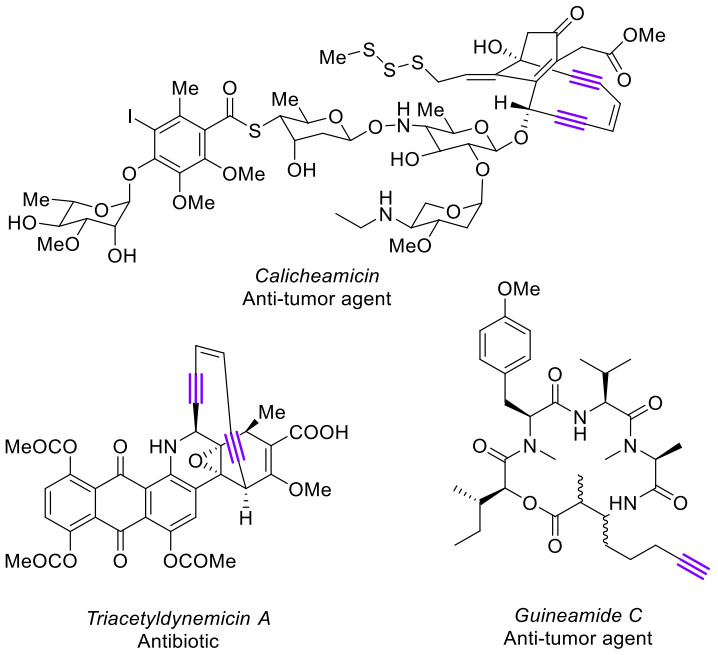
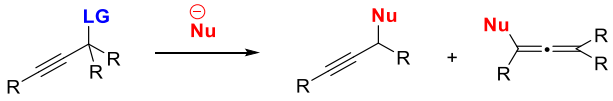


Figure 3-1: Alkyne containing natural products and pharmaceuticals.

However, when internal propargylic electrophiles are treated with nucleophiles in the presence of a metal-catalyst, there are two different reactive places, making the regioselectivity difficult to control (**Scheme *3-27***).[46]

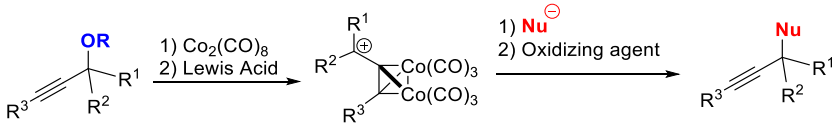
A.; Meltzer, L. T.; Wise, L. D.; Espitia, S. A.; Konkoy, C. S.; Whittemore, E. R.; Woodward, R. M. *J. Med. Chem.* **2000**, *43*, 3408-3419. d) Zhu, X.; Liu, J.; Zhang, W. *Nature Chemical Biology* **2015**, *11*, 115-120. e) Chai, Q. Y.; Yang, Z.; Lin, H. W.; Han, B. N.; *Mar. Drugs* **2016**, *14*, 216-233.

[46] a) Miyake, Y.; Uemura, S.; Nishibayashi, Y. *ChemCatChem* **2009**, *1*, 342-356. b) Detz, R. J.; Hiemstra, H.; van Maarseveen, J. H. *Eur. J. Org. Chem.* **2009**, 6263-6276. c) Zhang, D. Y.; Hu, X. P. *Tetrahedron Lett.* **2015**, *56*, 283-295.



Scheme 3-27: Propargylic substitution.

In 1977, Nicholas and co-workers reported that dicobalt hexacarbonyl-stabilized propargylic cations from propargylic alcohols could be trapped with a variety of nucleophiles. This reaction is known as Nicholas Reaction (**Scheme *3-28***).[47] Diastereoselective Nicholas reactions are possible, but the drawback of this transformation is that a full equivalent of $Co_2(CO)_8$ is needed.



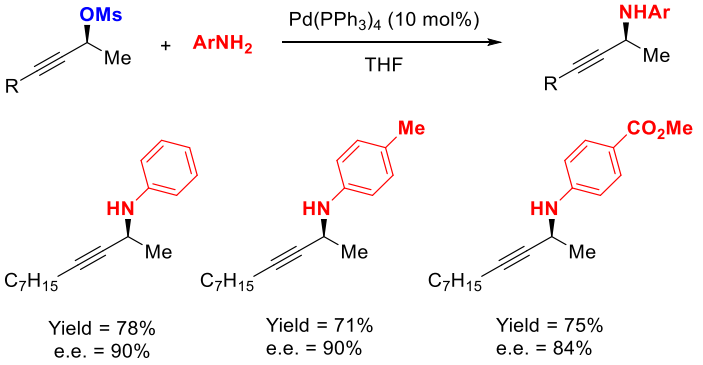
Scheme 3-28: Nicholas reaction.

The asymmetric propargylic substitution is an important challenge in synthetic chemistry. Although there are reports where the asymmetric propargylic substitution of terminal alkynes is achieved,[48] a comprehensive review of the literature exceeds the scope of the introduction of this chapter. Therefore, only literature concerning asymmetric propargylic substitution of internal alkynes will be included in this section.

[47] a) Lockwood, R. F.; Nicholas, K. M. *Tetrahedron Lett.* **1977**, 4163-4166. b) Kurti, L.; Czako, B. *Strategic Applications of Named Reactions in Organic Synthesis.* 2005, Elsevier Academic Press, London.

[48] a) Zhang, D. -Y.; Hu, X. P. *Tetrahedron Lett.* **2015**, *56*, 283-295. b) Roy, R.; Saha, S. *RSC Adv.* **2018**, *8*, 31129-31193.

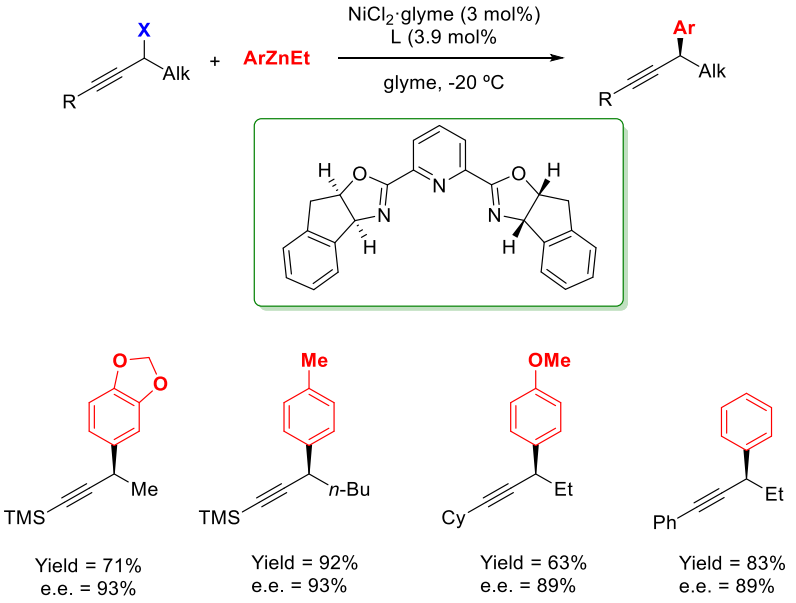
Despite the fact that palladium-catalyzed propargylic substitution usually gives the allenyl compound,[49] in 1996 Marshall and Wolf reported the propargylic substitution of enantiomerically pure mesylates with arylamines. The stereospecificity of the reaction was good and the reaction occurred with retention of the configuration (**Scheme *3-29***).[50]



Scheme 3-29: Palladium-catalyzed propargylic substitution.

In 2008, Smith and Fu reported the very first enantioselective Negishi cross-coupling of propargylic halides with arylzinc reagents using a chiral nickel/Pybox complex. The reaction worked well with both propargyl bromides and chlorides and the enantiomeric excesses were good to excellent (**Scheme *3-30***).[51]

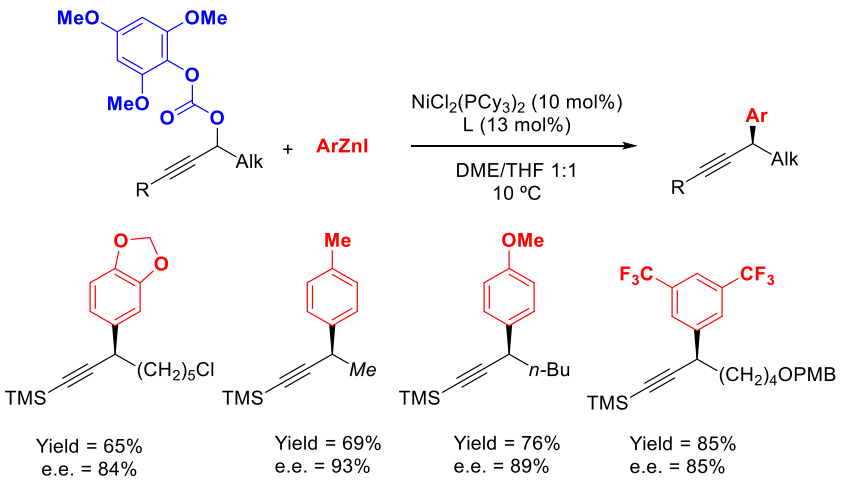
[49] a) Keinan, E.; Bosch, E. *J. Org. Chem.* **1986**, 51, 4006-4016. b) Tsuji, J.; Mandai, T. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2589-2612.
[50] Marshall, J. A.; Wolf, M. A. *J. Org. Chem.* **1996**, *61*, 3238-3239.
[51] Smith, S. W.; Fu, G. C. *J. Am. Chem. Soc.* **2008**, *130*, 12645-12647.



Scheme 3-30: Nickel-catalyzed Negishi cross-coupling of propargylic halides.

In 2012, the same group reported the enantioselective nickel-catalyzed Negishi cross-coupling of different propargylic compounds bearing a carbonate as leaving group. They used the same pybox ligand and readily available arylzinc reagents (**Scheme *3-31***).[52] This was the first report that performed an enantioselective sp_3-sp_2 cross-coupling using oxygen based electrophiels excluding allylic compounds.

[52] Oelke, A. J.; Sun, J.; Fu, G. C. *J. Am. Chem. Soc.* **2012**, *134*, 2966-2969.

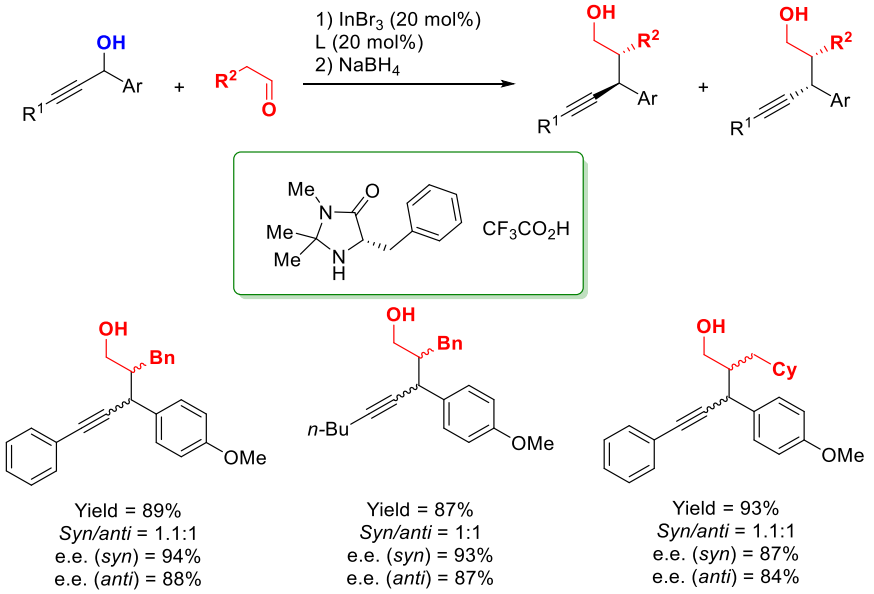


Scheme 3-31: Nickel-catalyzed Negishi cross-coupling of propargylic carbonates.

Nishibayashi and co-workers reported in 2011 a cooperative catalytic system for the propargylic substitution of alcohols with aldehydes. They used indium(III) bromide as Lewis acid and a chiral organocatalyst to achieve high levels of enantiocontrol. However, the diastereocontrol was not as high, and they obtained mixtures of the *syn* and the *anti*-isomers almost in equal proportion (**Scheme *3-32***).[53] The same year, Cozzi and co-workers reported the same transformation with slightly better results using indium(III) triflate and Macmillan catalyst. However, diastereoselectivity remained a problem.[54]

[53] Motoyama, K.; Ikeda, M.; Miyake, Y.; Nishibayashi, Y. *Eur. J. Org. Chem.* **2011**, 2239–2246.

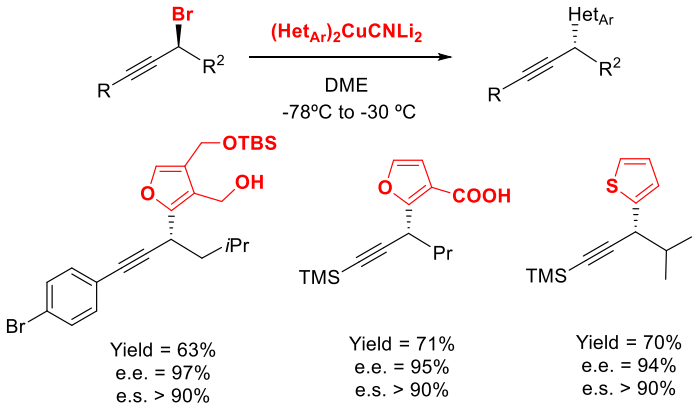
[54] Sinisi, R.; Vita, M. V.; Gualandi, A.; Emer, E.; Cozzi, P. G. *Chem. Eur. J.* **2011**, *17*, 7404-7408.



Scheme 3-32: Cooperative catalytic propargylic substitution of alcohols with aldehydes.

In 2016, Trost and co-workers reported the stereospecific propargylic substitution of propargylic bromides with hetereoaryl diorganocuprates (**Scheme *3-33***).[55] They obtained excellent yields and stereospecificities. However, a full equivalent of copper(I) salt was needed.

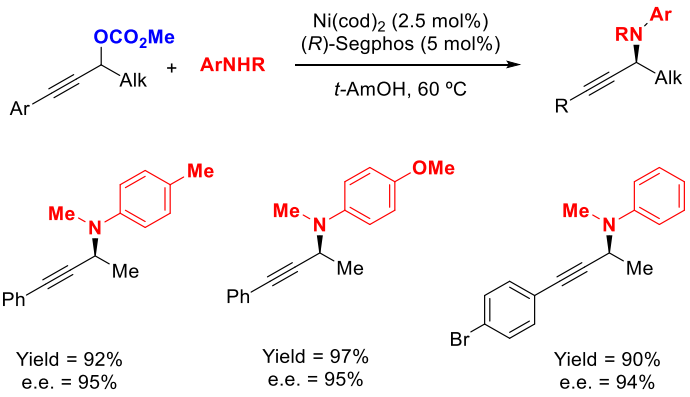
[55] Trost, B. M.; Debien, L. *Chem. Sci.* **2016**, *7*, 4985-4989.



Scheme 3-33: Stereospecific substitution of propargylic bromides.

Recently, Tsuji, Kawatsura and co-workers have reported the enantioselective propargylic amination of carbonates catalyzed by a chiral nickel-complex with excellent yields and enantioselectivities (**Scheme *3-34***).[56]

[56] Watanabe, K.; Miyazaki, Y.; Okubo, M.; Zhou, B.; Tsuji, H.; Kawatsura, M. *Org. Lett.* **2018,** *20*, 5448−5451.



Scheme 3-34: Nickel-catalyzed enantioselective amination of propargylic carbonates.

3.1.4. Stereospecific Copper-Catalyzed Synthesis of Allenes.

Although in 1875 Van't Hoff predicted the correct structure of allenes,[57] they were considered mere curiosities for a long period of time and its chemistry did not really starting to develop until the 50's.[58] Advances in the synthesis, characterization and isolation of this unique structures, especially in their enantiomerically pure form, have opened the door to the development of a huge variety of procedures to take advantage of their unique reactivity.[59]

Now, more than 150 natural products are known to have an allene in their structure, most of them enantiomerically enriched. There are important moieties in a wide variety of compounds. Some of the most

[57] Van't Hoff, J. H. *La Chimie dans L'Espace*, Bazendijk, Rotterdam, 1875.
[58] Taylor, D. R. *Chem. Rev*. **1967**, *67*, 317-359.
[59] a) Zimmer, R.; Dinesh, C. U.; Nandanan E.; Khan, F. A. *Chem. Rev*. **2000**, *100*, 3067-3125. b) Hashmi, A. S. K. *Angew. Chem. Int. Ed*. **2000**, *39*, 3590-3593. c) Ma, S. *Acc. Chem. Res*. **2003**, *36*, 701-712. d) *Modern Allene Chemistry*, Krause, N.; Hashmi, A. S. K. ed. Wiley-VCH, Weinheim, Germany, 2004. e) Hoffmann-Röder A.; Krause, N. *Angew. Chem. Int. Ed.* **2004**, *43*, 1196-1216. f) Ma, S. *Chem. Rev.* **2005**, *105*, 2829-2872. g) Ma, S. *Acc. Chem. Res*. **2009**, *42*, 1679-1688. h) Yu, S.; Ma, S. *Angew. Chem. Int. Ed*. **2012**, *51*, 3074-3112. i) Pullis, A. P.; Yeung, K.; Procter, D. J. *Chem. Sci*. **2017**, *8*, 5240-5247.

known allene-containing natural product and pharmaceuticals are fucoxanthin (the most abundant carotinoid), isolated from algae and diatomees,[60] grasshoper ketone, a metabolite of many carotinoids,[61] laurallene, a bromoallene isolated from red algae,[62] and Enprostil, a commercially marketed drug which is a highly potent inhibitor of gastric HCl secretion (**Figure *3-2***).[63]

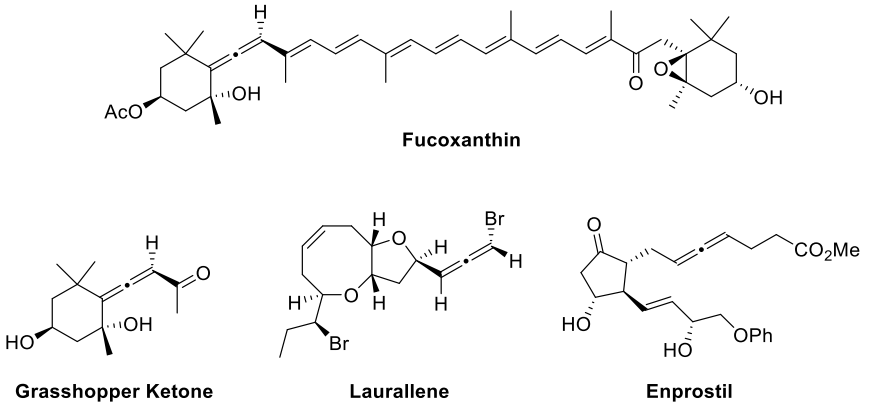


Figure 3-2: Natural products and drugs with an allene in their structure.

[60] a) Willstätter, R.; Page, H. J. *Justus Liebigs Ann. Chem*. **1914**, *404*, 237-271. b) Bonnett, R.; Spark, A. A.; Tee, J. L.; Weedon, B. C. L. *Proc. Chem. Soc. London* **1964**, *419*.

[61] a) Meinwald, J.; Erickson, K.; Hartshorn, M.; Meinwald, Y. C.; Eisner, T.; *Tetrahedron Lett*. **1968**, 2959-2962. b) DeVille, T. E.; Hursthouse, M. B.; Russell, S. W.; Weedon, B. C. L. *J. Chem. Soc. Chem. Commun*. **1969**, 754-755.

[62] a) Fukuzawa, A.; Kurosawa, E. Tetrahedron Lett. 1979, 2797-2800. b) Suzuki, M.; Koizumi, K.; Kikuchi, H.; Suzuki, T.; Kurosawa, E. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 715-718. c) Wright, A. D.; Koenig, G. M.; Sticher, O. *J. Nat. Prod.* **1991**, *54*, 1025-1033.

[63] Collins, P.W.; Djuric, S. W. *Chem. Rev.* **1993**, *93*, 1533-1564.

Among the methodologies to prepare allenes, one of the most convenient and straightforward strategies is the reaction of organocuprates generated from organolithium or organomagnesium reagents.[64]

Most of the existing procedures used stochiometric amounts of copper in the reaction, and there are few reported catalytic strategies.[65] This methodology presents several limitations, especially in catalytic asymmetric synthesis. Enantioselective methodologies do not offer a broad scope and minimum variation in the stereoelectronic properties of the propargylic compounds could lead to problems in the regio- and the stereoselectivity.[66] Also, the chirality transfer in stereospecific reaction is usually poor and the loss of enantiomeric purity is reported in the literature.[67]

In 2011, Sawamura and coworkers overcame these problems. They reported the synthesis of enantiomerically enriched allenes by a stereospecific copper-catalyzed γ-selective coupling of propargylic phosphonates and alkylboranes.[68] They did not need any ligand and had a wide scope. They demonstrated the transfer of chirality on 3 examples, obtaining excellent results (**Scheme *3*-*35***, top). A year later, they extended this methodology to alkenyl- and arylboronates (**Scheme *3*-*35***, bottom).[69]

[64] a) Hoffmann-Röder, A.; Krause, N. *Angew. Chem. Int. Ed*. **2002**, *41*, 2933-2935. b) Yu, S.; Ma, S. *Chem. Commun*. **2011**, *47*, 5384-5418. c) Neff, R. K.; Frantz, D. E. *ACS Catal*. **2014**, *4*, 519-528.

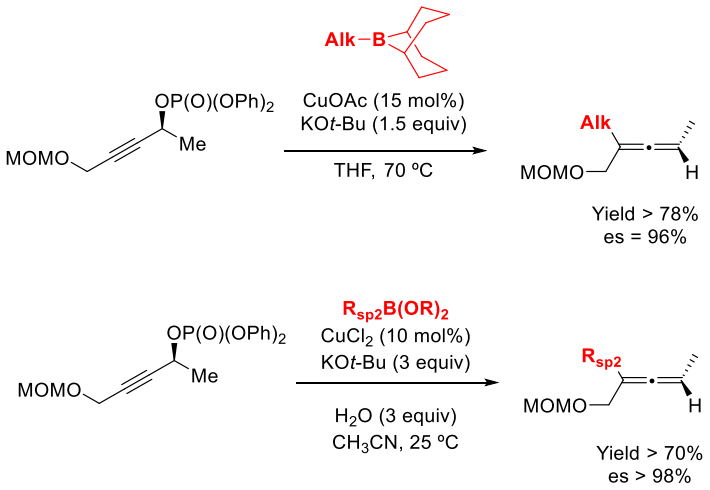
[65] For selected examples: a) Friel, D. F.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc*. **2008**, *130*, 9942-9951. b) Cerat, P.; Gritsch, P. J.; Goudreau, S. R.; Charette, A. B. *Org. Lett*. **2010**, *12*, 564-567.

[66] For selected examples: a) Alexakis, A.; Marek, I.; Mangeney, P.; Normant, J. F. *J. Am. Chem. Soc*. **1990**, *112*, 8042-8047. b) Li, H.; Grassi, D.; Guenee, L.; Bürgi, T.; Alexakis, A. *Chem. Eur. J*. **2014**, *20*, 16694-16706. c) Li, H.; Müller, D.; Guenee, L.; Alexakis, A. *Org. Lett*. **2012**, *14*, 5880-5883. d) Han, J. T.; Yun, J. *Chem. Commun*. **2019**, *55*, 9813-9816.

[67] a) Claesson, A.; Olsson, L. I.; *J. Chem. Soc. Chem. Commun*. **1979**, 524-525. b) Chenier, J. H. B.; Howard, J. A.; Mile, B. *J. Am. Chem. Soc*. **1985**, *107*, 4190-4191.

[68] Ohmiya, H.; Yokobori, U.; Makida, Y.; Sawamura, M. *Org. Lett*. **2011**, *13*, 6312-6315.

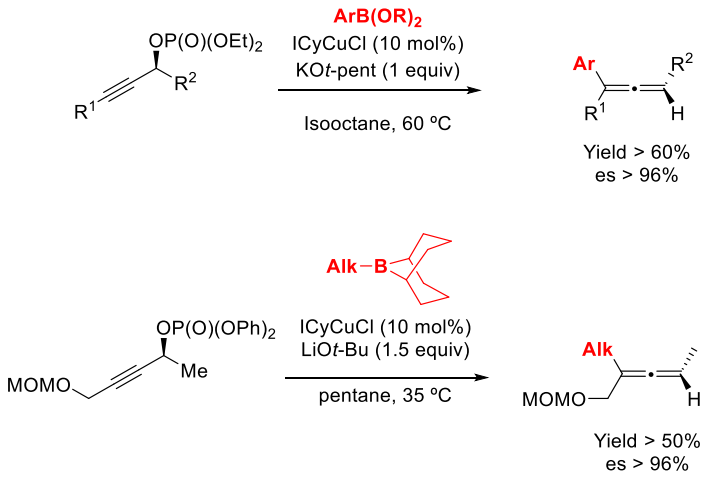
[69] Yang, M.; Yokokawa, N.; Ohmiya, H.; Sawamura, M. *Org. Lett*. **2012**, *14*, 816-819.



Scheme 3-35: Stereospecific copper-catalyzed coupling of propargylic phosphonates with boron reagents.

In the same year, Lalic and coworkers, develop a similar strategy where they performed the copper-catalyzed cross-coupling of propargylic phosphates and boron reagents to synthetize enantiomerically pure allenes (**Scheme *3-36***).[70] They used aryl boronates and alkyl boranes along a *N*-heterocyclecarbene copper-complex to obtain trisubstituted allenes with excellent results in yield and stereospecificity. They demonstrated by a stochiometric experiment with ICyCuMe, that the formal nucleophile is an organocopper reagent.

[70] Uehling, M. R.; Marionni, S. T.; Lalic, G. *Org. Lett*. **2012**, *14*, 362-365.



Scheme 3-36: Stereospecific copper-catalyzed cross-coupling reaction of propargylic phosphonates and boron reagents.

3.2. Regio- and Stereospecific Copper-Catalyzed Substitution Reaction of Propargylic Ammonium Salts with Aryl Grignard Reagents.

3.2.1. Introduction and objectives.

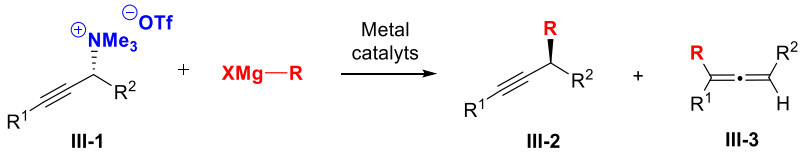
At the outset of our investigation, there were only three examples in the literature of a stereospecific transformation using ammonium salts as eletrophiles.[21,22,23] Additionally, only aryl and benzylic ammonium salts had been used in cross-coupling reactions. Moreover, most of the reported examples required the use of the air-sensitive and thermally unstable $Ni(COD)_2$ while the use of copper as catalyst was virtually unexplored.[28,29] With these precedents, we decided to contribute to the field with two objectives in mind: to expand the scope of the ammonium salts, with special interest in stereospecific transformations, and to introduce copper-catalysis in the arena.

We envisioned that propargylic ammonium salts would be good candidates to explore a stereospecific copper-catalyzed transformation (**Scheme *3-37***). To prepare these electrophiles, we could take advantage of the variety of methodologies existing in the literature to synthesize enantiomerically enriched propargylic amines, either from propargylic alcohols[71] or through different asymmetric catalytic methods.[72] The specific objective of this chapter is to develop a stereospecific Kumada type cross-coupling of propargylic ammonium salts with Grignard reagents, finding

[71] a) Matsumura, K.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1997**, *119*, 8738-8739. b) Anand, N.K.; Carreira, E.M. *J. Am. Chem. Soc.* **2001**, *123*, 9687-9688. c) Takita, R.; Yakura, K.; Ohshima, T.; Shibasaki, M. *J. Am. Chem. Soc.* **2005**, *127*, 13760-13761.

[72] a) Gommermann, N.; Koradin, C.; Polborn, K.; Knochel, P. *Angew. Chem., Int. Ed.* **2003**, *42*, 5763-5766. b) Akullian, L.C.; Snapper, M.L.; Hoveyda, A.H. *Angew. Chem., Int. Ed.* **2003**, *42*, 4244-4247. c) Knöpfel, T.F.; Aschwanden, P.; Ichikawa, T.; Watanabe, T.; Carreira, E.M. *Angew. Chem., Int. Ed.* **2004**, *43*, 5971-5973. d) Klauber, E.G.; De, C.K.; Shah, T.K.; Seidel, D. *J. Am. Chem. Soc.* **2010**, *132*, 13624-13626. e) Paioti, P.H.S.; Abboud, K.A.; Aponick, A. *J. Am. Chem. Soc.* **2016**, *138*, 2150-2153.

the optimal catalytic system to control the stereospecificity and the regioselectivity.



Scheme 3-37: Objectives of this chapter.

3.2.2. Synthesis of Starting Materials.

First, we prepared a series of propargylic ammonium salts **III-1** (**Figure *3-3***). We prepare them by different procedures and in the next pages we will explain each of the corresponding methodologies.

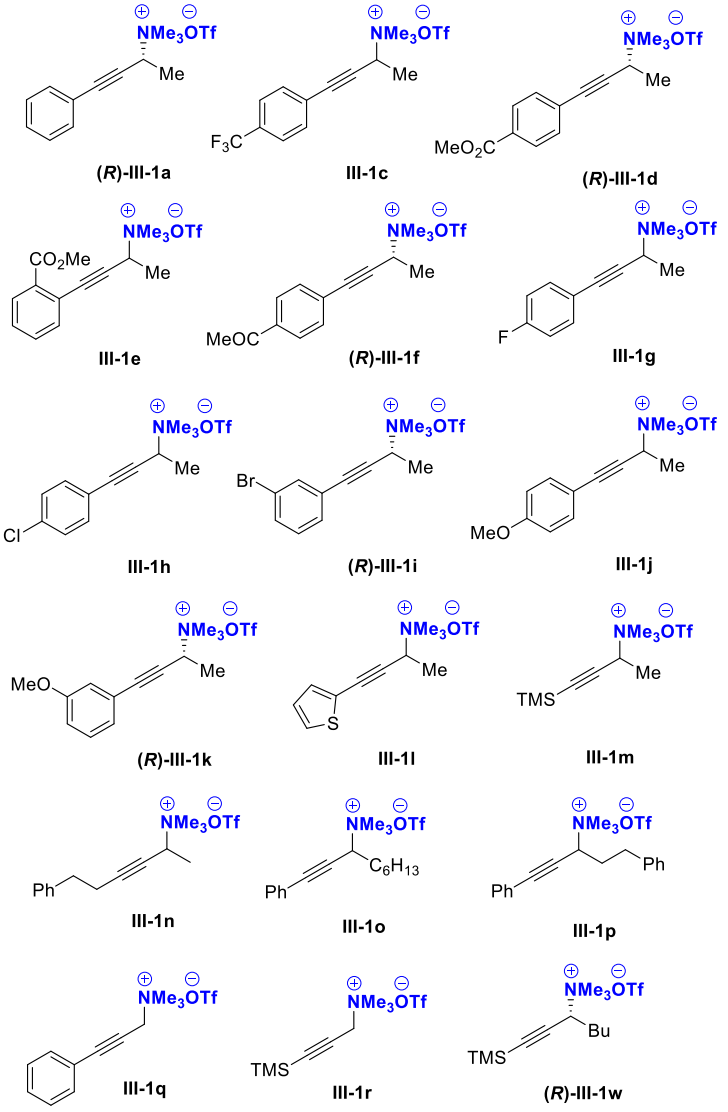
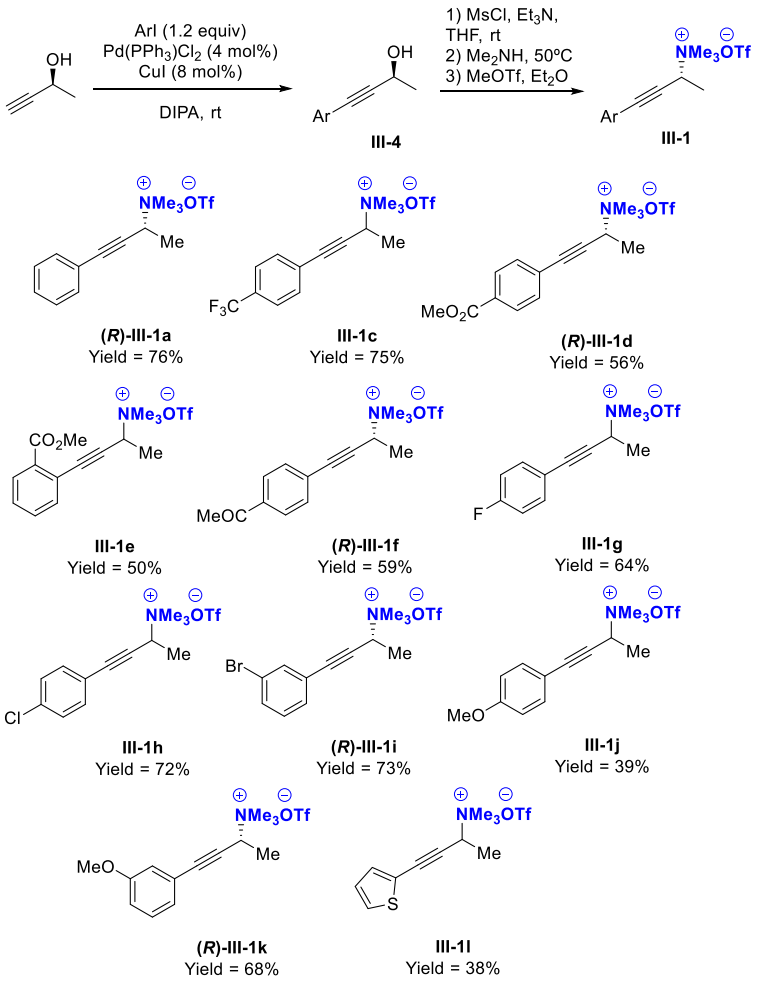


Figure 3-3: Prepared propargylic ammonium salts.

We choose propargylic ammonium salt **(*R*)-III-1a** as model substrate to study the reaction. This compound could be synthetized starting with a Sonogashira reaction between (*S*)-3-butyn-2-ol and phenyl iodine. After that, a one-pot mesylation/amination with dimethylamine, followed by

treatment with methyl triflate yielded the enantiomerically enriched ammonium salt with 76% of global yield (**Scheme *3-38***). We use the same procedure to prepare **III-1c-l**.



Scheme 3-38: Synthesis of propargylic ammonium salt starting by Sonogashira reaction.

The absolute configuration of (*R*)-**III-1i** was determined from single crystal X-ray crystallography (**Figure *3-4***).[73] The absolute configuration of all the other propargylic ammonium salts was assigned by analogy.

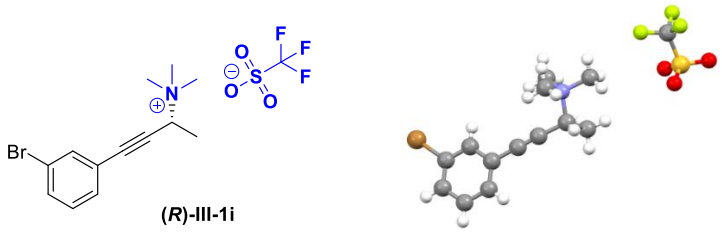
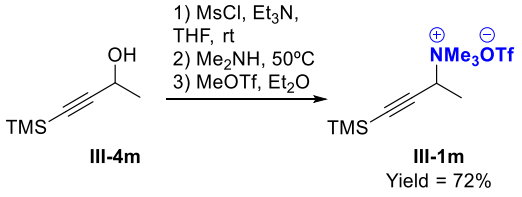


Figure 3-4: Single X-ray structure of (*R*)-III-1i.

To synthetize **III-1m**, we started with the commercially available -(Trimethylsilyl)-3-butyn-2-ol and then proceeded with the same route of one-pot mesylation/amination, followed by treatment with methyl triflate (**Scheme *3-39***).

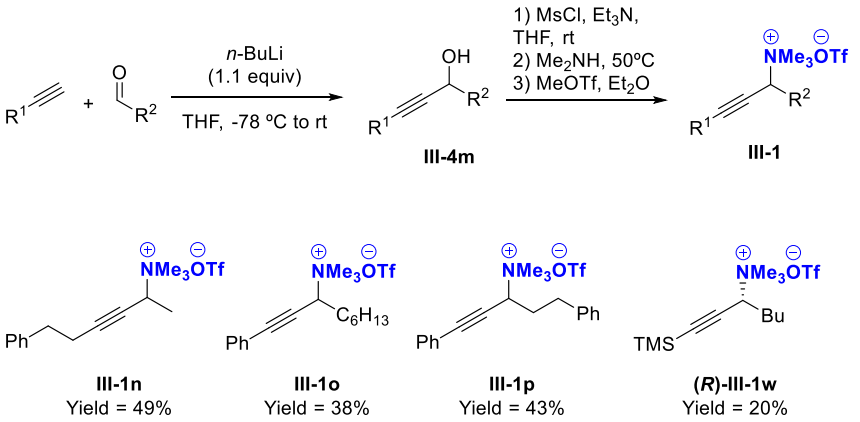


Scheme 3-39: Synthesis of **III-1m**.

For the synthesis of **III-1n**, **III-1o**, **III-1p and III-1w** we started with a nucleophilic attack of a lithium acetylide to an aldehyde, followed by the

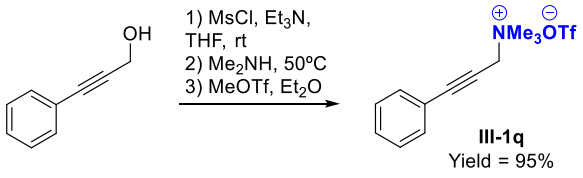
[73] CCDC 1546939 contains the supplementary crystallographic data. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html

same sequence as before (**Scheme *3-40***). In the case of **III-1w**, we made a kinetic resolution to obtain the enantiomerically enriched alcohol.



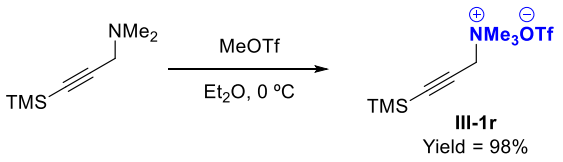
Scheme 3-40: Synthesis of **III-1n**, **III-1o**, **III-1p** and **(*R*)-III-1w**.

Primary propargylic ammonium salt **III-1q** was prepared from corresponding commercially available alcohol, through one-pot mesylation/amination, followed by treatment with methyl triflate (**Scheme *3-41***).



Scheme 3-41: Synthesis of **III-1q**.

Finally, ammonium salt **III-1r**, was synthesized by treatment of the commercially available dimethylamine with methyl triflate (**Scheme *3-42***).



Scheme 3-42: Synthesis of **III-1r**.

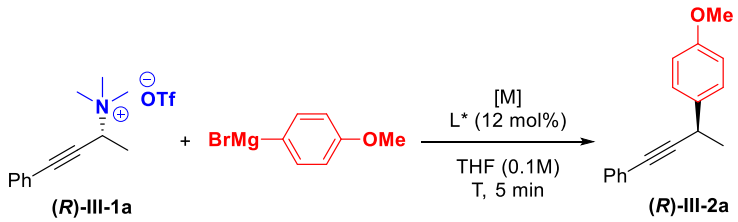
3.2.3. Copper-Catalyzed Substitution Reaction of Propargylic Ammonium Salts. Screening of Conditions.

Motivated by the possibilities of this reaction, we choose the previously reported conditions for palladium catalyzed Kumada coupling of aryl trimethylammonium salts as a starting point. When we treated compound **(*R*)-III-1a** with 4-methoxyphenylmagnesium bromide and $Pd(PPh_3)_2Cl_2$ we observed the formation of a 40:60 mixture of **III-2a** and **III-3a** in 12% yield (**Table *3-1***, entry 1). Far from assuming that the desired reaction did not work, we got more motivated about finding the right catalytic system for our reaction.

We started our screening by changing the catalyst to $[Ni(dppe)]Cl_2$ and surprisingly the formation of the allenyl product is completely avoided, although the yield was low and we observed the formation of the corresponding propargylic bromide (**Table *3-1***, entry 2). Based on our previous experience in copper catalysis we decided to use $Cu(CH_3CN)_4PF_6$ along with the phosphine Xanthphos. Surprisingly, the desired product was formed in good yield and good stereoselectivity with no trace of the allenyl product (**Table *3-1***, entry 3). With this result in hand, we decided to try a battery of different ligands. All ligands tested gave the α-product with good

to excellent yields and good stereospecificity (**Table *3-1***, entries 4-14). Surprisingly, when we tried the reaction without any added ligand, the α-product was formed with 98% yield and 98% of enantiomeric ratio (**Table *3-1***, entry 15). Changing the copper source to copper(I) chloride yield the product with inferior result (**Table *3-1***, entry 16). We could reduce the catalytic loading to 5 mol% with a slight decrease in the yield (**Table *3-1***, entry 17), but switching the solvent to CH_2Cl_2 gave 98% yield again with only 5 mol% of copper (**Table *3-1***, entry 18). Finally, the reaction did not work without catalyst at -40 ºC. Interestingly, at room temperature the α-product was obtained inlow yield and almost complete erosion of the stereospecificity (**Table *3-1***, entry 19).

Table 3-1: Influence of the metal source and the ligand.

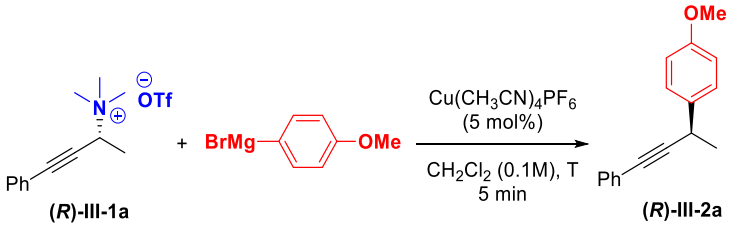


Entry	[M] (mol%)	L	T (ºC)	Yield[c] (%)	e.r.[d]
1[a]	$Pd(PPh_3)Cl_2$ (10)	----	rt	12	----
2[b]	$[Ni(dppe)]Cl_2$ (10)	----	rt	22	----
3	$Cu(CH_3CN)_4PF_6$ (10)	Xantphos	-40	80	93:7
4	$Cu(CH_3CN)_4PF_6$ (10)	PCy_3	-40	85	97.5:2.5
5	$Cu(CH_3CN)_4PF_6$ (10)	Sphos	-40	89	98.2
7	$Cu(CH_3CN)_4PF_6$ (10)	IMes	-40	89	97:3
8	$Cu(CH_3CN)_4PF_6$ (10)	Bathophenanthroline	-40	93	98:2
9	$Cu(CH_3CN)_4PF_6$ (10)	PPh_3	-40	80	98:2
10	$Cu(CH_3CN)_4PF_6$ (10)	dppe	-40	80	97:3
11	$Cu(CH_3CN)_4PF_6$ (10)	dppp	-40	63	97.5:2.5
13	$Cu(CH_3CN)_4PF_6$ (10)	dppf	-40	61	88:12
14	$Cu(CH_3CN)_4PF_6$ (10)	4-4'-ditBu-bpy	-40	72	96:4
15	$Cu(CH_3CN)_4PF_6$ (10)	-----	-40	98	99:1
16	CuCl (10)	-----	-40	80	85:15
17	$Cu(CH_3CN)_4PF_6$ (5)	-----	-40	95	99:1
18[e]	**$Cu(CH_3CN)_4PF_6$ (5)**	-----	**-40**	**98**	**99:1**
19[e]	-----	-----	rt	22	54:46

Reaction condition: **(*R*)-III-1a** (0.1 mmol, 1.0 equiv), ArMgX (1.1 equiv), CuX (10 mol%), THF (0.1 M), −40 °C, 5 min, unless otherwise noted. [a]Reaction conditions: $Pd(PPh_3)_2Cl_2$ (10 mol%), 4 h. 40:60 mixture of **III-2a** and **III-3a** was obtained. [b] $[Ni(dppe)]Cl_2$ (10 mol%), 4 h. [c]Isolated yield after column chromatography. [d]Determined by chiral SFC. [e] CH_2Cl_2 was used instead of THF.

Next, we tested the influence of the temperature (**Table *3-2***). We observed that increasing the temperature caused a decrease in both the yield and the enantiomeric excess (**Table *3-2***, entries 2 and 3).

Table 3-2: Influence of the temperature.

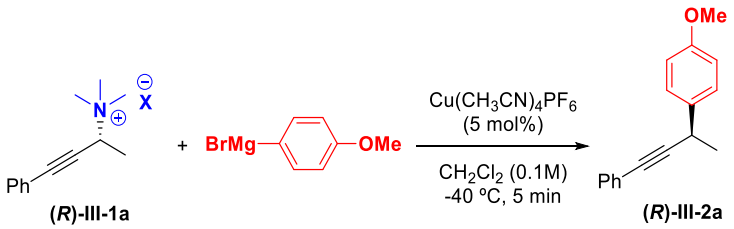


Entry	T (ºC)	Yield[a] (%)	e.r.[b]
1	**-40**	**98**	**99:1**
2	-20	96	95:5
3	0	94	94:6

Reaction conditions: ***(R)*-III-1a** (0.1 mmol, 1.0 equiv), ArMgX (1.1 equiv), $Cu(CH_3CN)_4PF_6$ (5 mol%), CH_2Cl_2 (0.1 M), 5 min, unless otherwise noted. [a]Isolated yield after column chromatography. [b]Determined by chiral SFC.

We next explored the influence of the counteranion in the outcome of the transformation (**Table *3-3***). Switching from triflate to mesylate the yield dropped significantly and the enantiomeric excess decreased slightly (**Table *3-3***, entry 2). The use of tetrafluoroborate or iodine afforded similar results as those observed with the mesylate (**Table *3-3***, entries 3-4). Finally, the use of tosylate as counteranion preserved the enantiomeric excess but with lower yield (**Table *3-3***, entry 5).

Table 3-3: Influence of the nature of the counteranion.

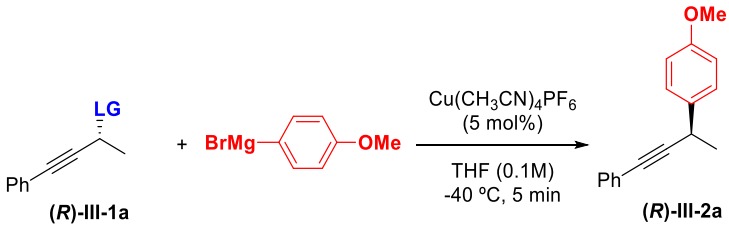


Entry	X	Yield (%)[a]	e.r.[b]
1	**OTf**	**90**	**99:1**
2	**OMs**	58	94:6
3	**BF_4**	68	94:6
4	**I**	58	96:4
5	**OTs**	56	98:2

Reaction conditions: **(*R*)-III-1a** (0.1 mmol, 1.0 equiv), ArMgX (1.1 equiv), $Cu(CH_3CN)_4PF_6$ (5 mol%), CH_2Cl_2 (0.1 M), 5 min, unless otherwise noted. [a]Isolated yield after column chromatography. [b]Determined by chiral SFC.

We next checked if the nature of the leaving group had any influence in the reaction (**Table *3-4***). Starting from a mesylate derivative we observed lower yield and some erosion of the stereospecificity (**Table *3-4***, entry 2). Phosphates provided an inseparable 95:5 mixture the α-product and the allenyl derivative (γ-product) (**Table *3-4***, entry 3). Finally, a propargylic acetate did not react under the optimized conditions (**Table *3-4***, entry 4).

Table 3-4: Influence of the leaving group.



Entry	X	Yield (%)[a]	α/γ [b]	e.r.[c]
1	**NMe_3OTf**	**90**	**≥98:2**	**99:1**
2	**OMs**	75	≥98:2	92:8
3	**$OP(O)(OEt)_2$**	84	95:5	98:2
4	**OAc**	NR		

Reaction conditions: **(*R*)-III-1a** (0.1 mmol, 1.0 equiv), ArMgX (1.1 equiv), $Cu(CH_3CN)_4PF_6$ (5 mol%), CH_2Cl_2 (0.1 M), 5 min, unless otherwise noted. [a]Isolated yield after column chromatography. [b]Determined by ^{1}H-NMR. [c]Determined by chiral SFC.

These preliminary results were interesting for different reasons. The products are very attractive synthetic intermediates. They contain a benzylic stereocenter, present in a wide number of biologically active compounds,[74] and an alkyne which is an extremely versatile functional

[74] For selected examples, see: (a) Yu, K. -L.; Spinazze, P.; Ostrowski, J.; Currier, S. J.; Pack, E. J.; Hammer, L.; Roalsvig, T.; Honeyman, J. A.; Tortolani, D. R.; Raczek, P. R.; Mansuri, M. M.; Starrett, J. E., Jr. *J. Med. Chem.* **1996**, *39*, 2411. (b) Johnson, D. S.; Ahn, K.; Kesten, S.; Lazerwith, S. E.; Song, Y.; Morris, M.; Fay, L.; Gregory, T.; Stiff, C.; Dunbar, J. B., Jr.; Liimatta, M.; Beidler, D.; Smith, S.; Nomanbhoy, T. K.; Cravatt, B. F. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 2865. (c) Pereira, A. R.; Strangman, W. K.; Marion, F.; Feldberg, L.; Roll, D.; Mallon, R.; Hollander, I.; Andersen, R. J. *J. Med. Chem.* **2010**, *53*, 8523. (d) Mihalic, J. T.; Chen, X.; Fan, P.; Chen, X.; Fu, Y.; Liang, L.; Reed, M.; Tang, L.; Chen, J.-L.; Jaen, J.; Li, L.; Dai, K. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 7001.

group.[75] Moreover, the selective attack at the α-position is very unusual in copper-catalyzed cross-coupling reactions of propargylic electrophiles, in which the γ-carbon is usually the reactive site. Additionally, the reaction is extremely fast (5 min) at –40 ºC and only 1.1 equivalents of the Grignard reagent is needed. Therefore, it was reasonable to predict a broad functional group compatibility, despite the high reactivity of the nucleophiles.

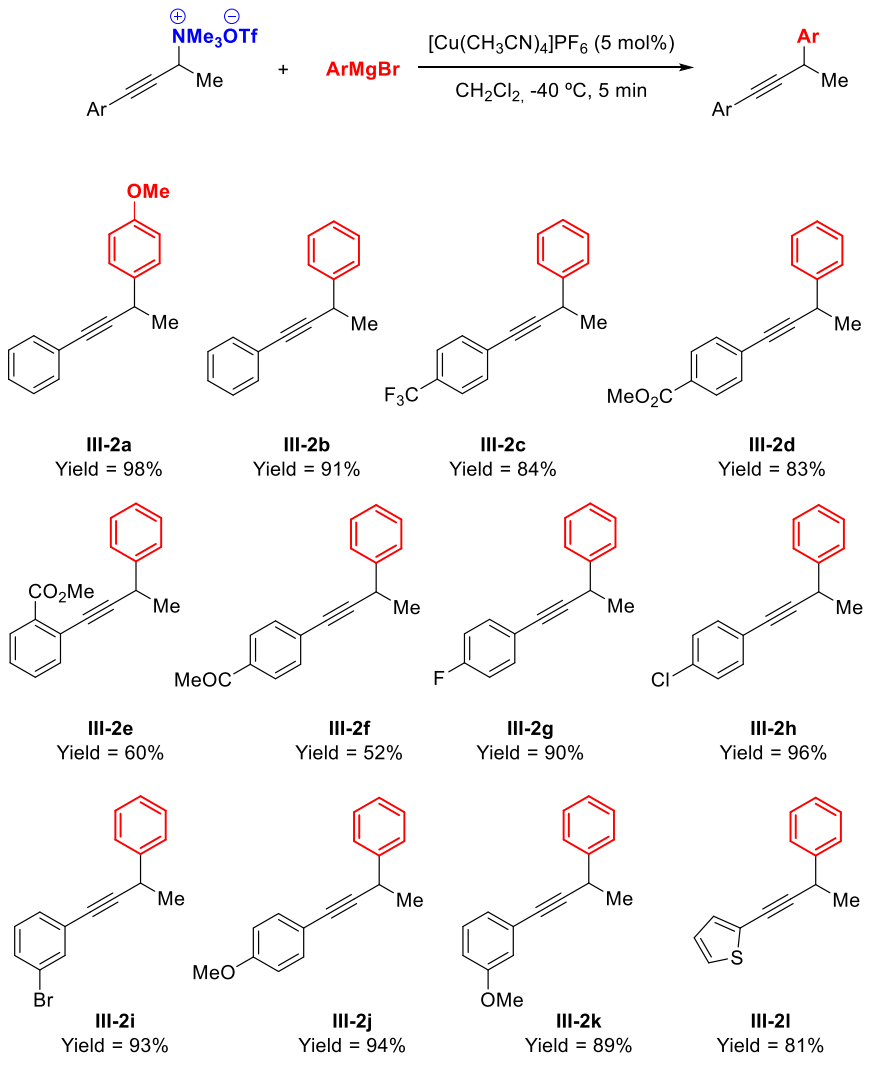
[75] (a) *Acetylene Chemistry*; Diederich, F., Stang, P. J., Tykwinski, R. R., Eds.; Wiley-VCH: New York, 2005. (b) *The Chemistry of Triple-Bonded Functional Groups*; Patai, S., Ed.; Wiley: New York, 1994.

3.2.4. Scope of the Reaction.

With the optimal conditions in hand, we next prepared a series of racemic secondary propargylic ammonium salts to determine the structural scope of the reaction (**Scheme *3-43*** and **Scheme *3-44***). Using phenyl magnesium bromide, we obtained compound **III-2b** with excellent results. The optimal conditions allowed a wide variety of functional groups in the aromatic ring (**III-2c-k**). Electron-withdrawing groups worked well with the reaction conditions (**III-2c-f**). The fact that the reaction was so fast at low temperature, using only 1.1 equivalents of the Grignard reagent, allowed the introduction of functional groups that are not usually compatible with strong nucleophiles. Ester groups were introduced in both *para* (**III-2d**) and *orto* positions (**III-2e**) without observing side reactions. Even ammonium salt **III-1f** with a ketone substituent in the aromatic ring was compatible with the reaction conditions. In this case, however, the chemoselectivity was not complete and we detected products derived from the attack of the Grignard reagent to the ketone in the crude mixture.

Propargylic ammonium salts containing aryl fluorides (**III-1g**), aryl chlorides (**III-1h**) and aryl bromides (**III-1i**) reacted exclusively at the propargylic position (compounds **III-2g**, **III-2h** and **III-2i**). Importantly, we performed the reaction with **III-1h** at gram scale with any significant decrease in the yield or the chemoselectivity.

We also carried out the reaction using propargylic compound with electron-donating groups in the aromatic ring. Methoxy substituents did not affect the yield neither at *para* (**III-2j**) or *meta* position (**III-2k**). Finally, heterocycles were also compatible with the reaction conditions and compound **III-2l** was obtained in excellent yield.



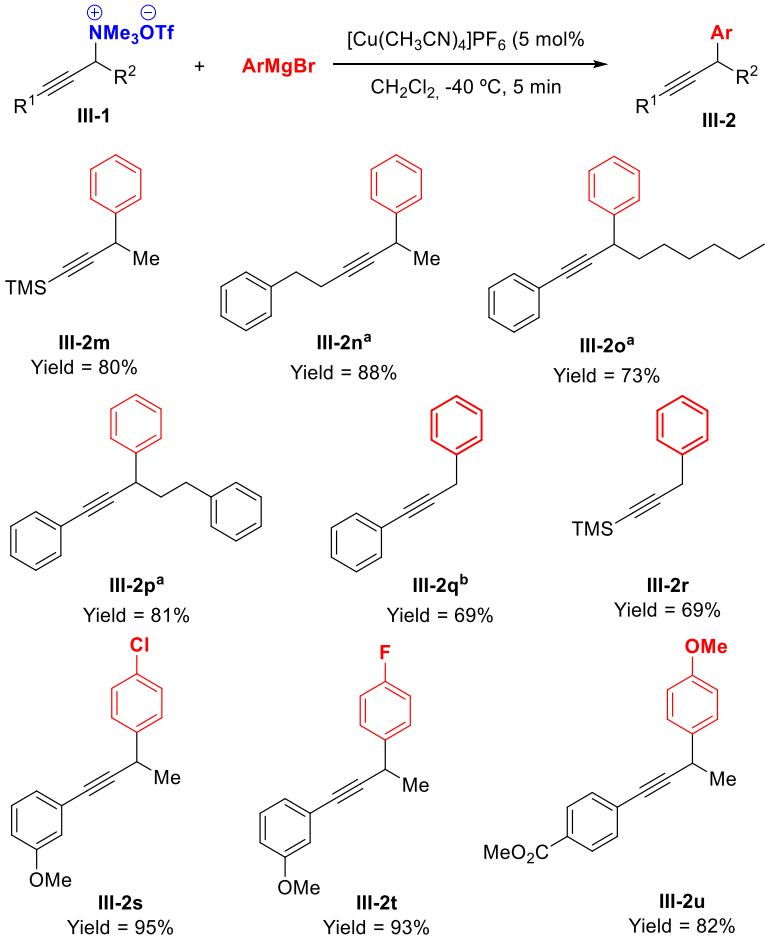
Scheme 3-43: Scope of the propargylic substitution of racemic ammonium salts.

Silyl (**III-2m**) and alkyl substitution (**III-2n**) in the acetylene moiety are also allowed under the reaction conditions. For compound **III-2n** we had to increase the catalytic loading to 10 mol% and decrease the concentration of the reaction to achieve good conversions. We also tried different alkyl chains in the propargylic position. We were delighted to see that

compounds **III-2o** and **III-2p** were obtained with excellent results. For this last two examples, we also had to increase the catalytic loading to 10 mol% and decrease the concentration. This lower reactivity could be caused by a subtle difference in the stereoelectronic effects of the substituent in the alkyne and the propargylic position.

Primary ammonium salts afforded only moderate results (**III-2q** and **III-2r**) and a competition experiment between ammonium salt **III-1a** and **III-1q** under the standard reaction conditions suggested that they are much less reactive than the secondary ones (see section **3.2.6**). The yield observed for compound **III-2q** increased from 50% to 69% yield when the reaction was carried out at room temperature.

The propargylic substitution also worked with different aryl magnesium bromides. Using aryl magnesium bromides with electron-withdrawing groups the desired products were prepared in good yields (**III-2s** and **III-2t**). The same was valid when we used a Grignard reagent with an electron-donating group (**III-2u**).



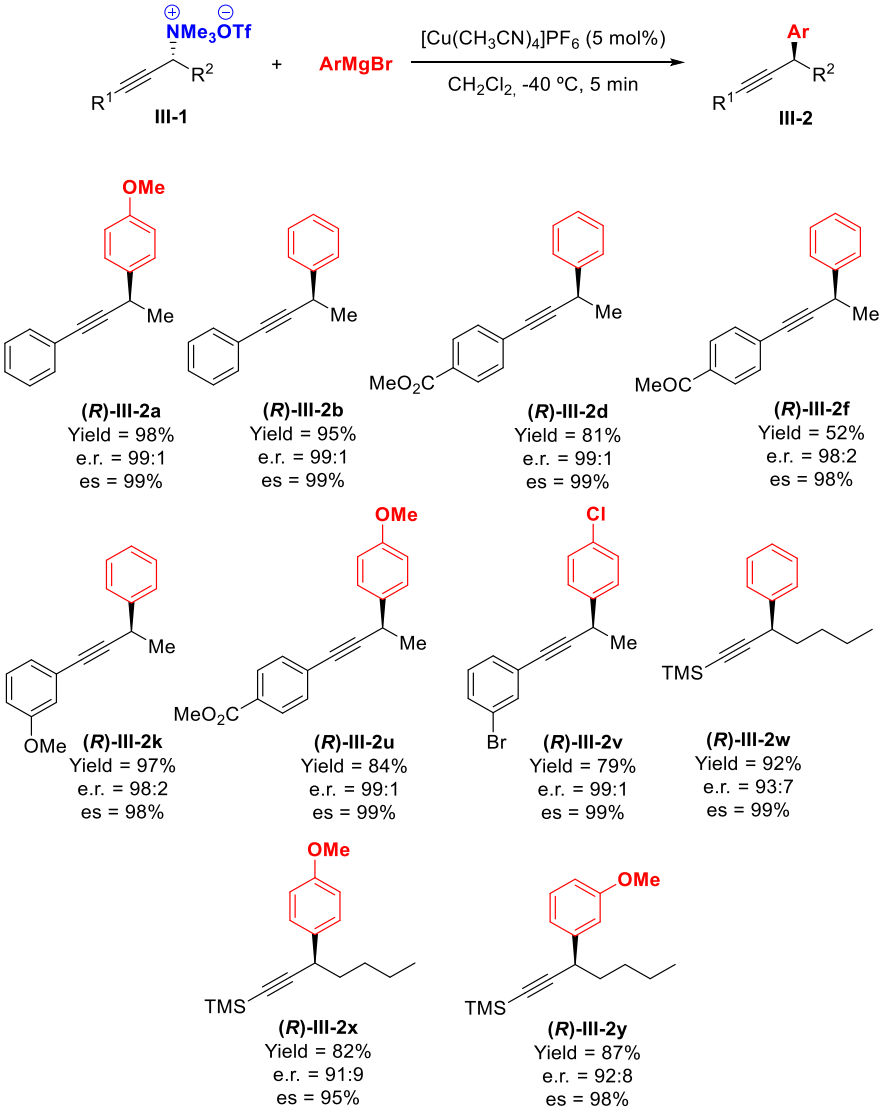
[a]$Cu(CH_3CN)_4PF_6$ (10 mol%), CH_2Cl_2 (0.03 M). [b] Reaction carried out at rt.

Scheme 3-44: Scope of the propargylic substitution of racemic ammonium salts.

3.2.5. Stereospecific Substitution.

During the optimization of the reaction conditions, we observed complete stereospecificity for compound **(*R*)-III-2a**. Therefore, the next step was to check if the chirality transfer was general for different ammonium salts and Grignard reagents. Ammonium salts with different aryl substitution such as, an ester group (**(*R*)-III-2d**), a ketone (**(*R*)-III-2f**) or a methoxy group (**(*R*)-III-2d**) gave the desired product with excellent results. Different Grignard reagents also gave good stereospecificity. Interestingly, we could prepare the enantiomerically enriched compound **(*R*)-III-2v**, with two different halides groups on the aromatic ring, which would be difficult to prepare using other transition metals.

Silyl substituted propargylic compound with an alkyl chain in the propargylic position were also suitable susbtrates for the reaction and compounds **(*R*)-III-2w, (*R*)-III-2x** and **(*R*)-III-2y** were prepared with excellent results.

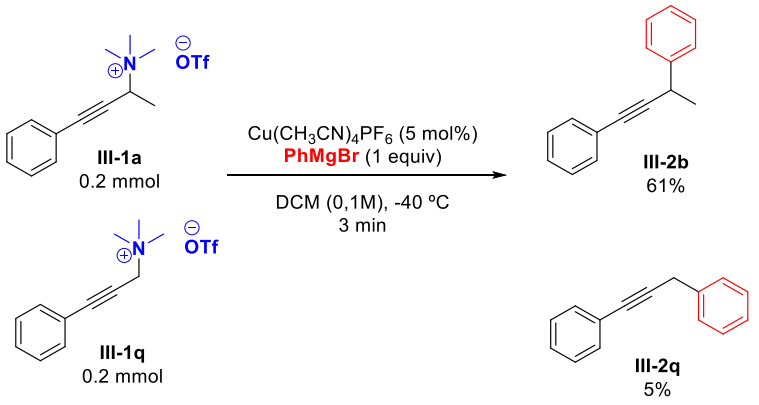


Scheme 3-45: Scope of the propargylic substitution of enantiomerically enriched ammonium salts.[76]

[76] Enantiospecifity (es) = (e.e.$_{product}$ / e.e.$_{starting\ material}$) * 100.

3.2.6. Competition experiment.

To test the different reactivity between primary and secondary ammonium salts we did a competition experiment (**Scheme *3-46***). We observed that secondary propargylic ammonium salts are much more reactive than the primary ones. Although we do not have a mechanism that explain the selectivity and reactivity observed, this result suggested that there could be a considerable amount of C-N bond cleavage in the transition state of the reaction.[77]



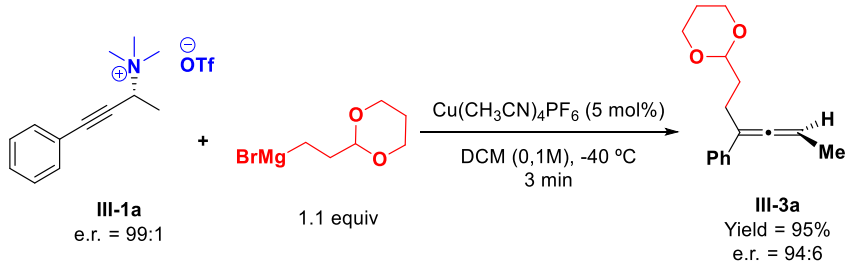
Scheme 3-46: Competition experiment between secondary and primary ammonium salts.

[77] Westaway, K. C.; Poirier, R. A. *Can. J. Chem.* **1975**, *53*, 3216-3226.

3.3. Regio- and Stereospecific Copper-Catalyzed Substitution Reaction of Propargylic Ammonium Salts with Aryl Grignard Reagents.

3.3.1. Introduction and Objectives.

When we tested for the first time our methodology but using an alkyl Grignard reagent, we were surprise to see that the regioselectivity change completely (**Scheme *3-47***). We obtained the corresponding allene with no trace of the propargylic compound in the reaction mixture.

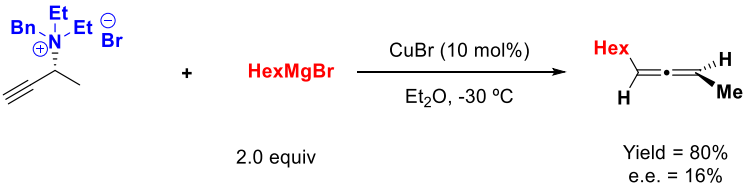


Scheme 3-47: First attempt on the propargylic substitution of propargylic ammonium salts with alkyl Grignard reagents.

We only knew one example of this kind of transformation. In 1979, Claeson and coworkers reported that an enantiomerically enriched propargylic ammonium bromide reacted with an alkyl Grignard reagent in an S_N2' fashion (**Scheme *3-48***).[78] It was an isolated example and they observe a significant erosion in the enantiomeric purity. During the development of this work, Ma and coworkers reported the synthesis of tetrasubstituted allenes using propargylic ammonium salts as starting

[78] Claesson, A.; Olsson, L. I. *Acta Chem. Scand*. **1979**, *B33*, 679-684.

materials.[43] However, they did not explore the possibilities of a stereospecific reaction.



Scheme 3-48: Copper-catalyzed substitution of propargylic ammonium salt.

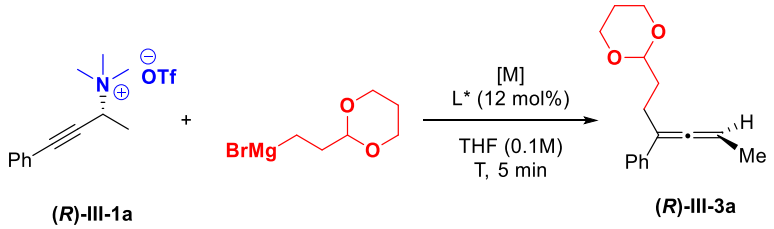
With these precedents, we decided to contribute to the field with an objective in mind: to expand the scope of the ammonium salts, with special interest in stereospecific transformations.

The specific objective of this chapter is to develop a stereospecific S_N2' substitution of propargylic ammonium salts with alkyl Grignard reagents, to form trisubstituted allenes. Also, we will have to find the optimal catalytic system to control the stereospecificity and the regioselectivity.

3.3.2. Copper-Catalyzed S_N2' Substitution Reaction of Propargylic Ammonium Salts. Screening of Conditions.

With the first result in hand (**Scheme *3-47*** and **Table *3-5***, entry 1), we decided to try different ligands to check for the best condition for this reaction (**Table *3-5***). First, we tried to use copper(I) chloride instead of $Cu(CH_3CN)_4PF_6$, however, the obtained result were inferior (**Table *3-5***, entry 2). Based on our previous experience in copper catalysis we decided to use the phosphine Xanthphos. We were happy to see that the results were better and we obtained allene **(*R*)-III-3a** with 86% yield and 96% of stereospecificity (**Table *3-5***, entry 3). With this result in hand, we decided to try a battery of different ligands. All ligands tested gave the γ-product with good to excellent yields and good stereospecificity (**Table *3-5***, entries 4-9). The best result was obtained using the phosphine Sphos. With this ligand, **(*R*)-III-3a** was obtained in 86% yield and 98% stereospecificity (**Table *3-5***, entry 9). We could reduce the catalytic loading to 5 mol%, obtaining the same result (**Table *3-5***, entry 10), and switching the solvent to CH_2Cl_2 gave slightly better result and rising the yield to 92% (**Table *3-5***, entry 11). Finally, the reaction did not work without catalyst at -40 ºC. Interestingly, at room temperature the γ-product was obtained in low yield and stereospecificity (**Table *3-5***, entry 13).

Table 3-5: Influence of the metal source and the ligand.



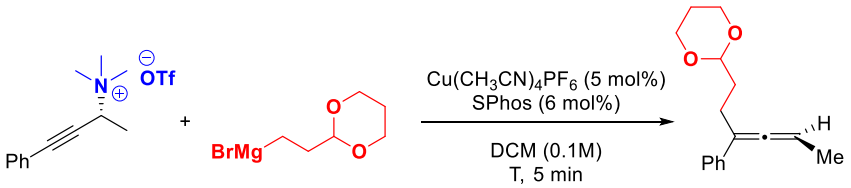
(*R*)-III-1a (*R*)-III-3a

Entry	[M] (mol%)	L	T (°C)	Yield[c] (%)	er[d]
1	$Cu(CH_3CN)_4PF_6$ (10)	-----	-40	95	94:6
2	CuCl (10)	-----	-40	82	86:14
3	$Cu(CH_3CN)_4PF_6$ (10)	Xantphos	-40	86	97:3
4	$Cu(CH_3CN)_4PF_6$ (10)	PCy_3	-40	70	96:4
5	$Cu(CH_3CN)_4PF_6$ (10)	(±)-BINAP	-40	94	97:3
6	$Cu(CH_3CN)_4PF_6$ (10)	Bathophenanthroline	-40	88	97:3
7	$Cu(CH_3CN)_4PF_6$ (10)	(±)-DTBM-Segphos	-40	94	97:3
8	$Cu(CH_3CN)_4PF_6$ (10)	dppf	-40	82	96:4
9	$Cu(CH_3CN)_4PF_6$ (10)	Sphos	-40	86	98.2
10[a]	$Cu(CH_3CN)_4PF_6$ (5)	Sphos	-40	86	98.2
11[a,b]	$Cu(CH_3CN)_4PF_6$ (5)	Sphos	-40	92	98.2
12	-----	-----	-40	----	----
13	-----	-----	rt	24	78:22

Reaction condition: **(*R*)-III-1a** (0.2 mmol, 1.0 equiv), AlkylMgX (1.1 equiv), CuX (10 mol%), Ligand (12 mol%), THF (0.1 M), −40 °C, 5 min, unless otherwise noted. [a]Using 6 mol% of ligand. [b]Using CH_2Cl_2 (0.1 M) as solvent. [c]Isolated yield after column chromatography. [d]Determined by chiral SFC.

Next, we tested the influence of the temperature (**Table *3-6***). We observed that increasing the temperature caused a decrease in both the yield and the enantiomeric excess (**Table *3-6***, entries 2 and 3).

Table 3-6: Influence of the temperature.



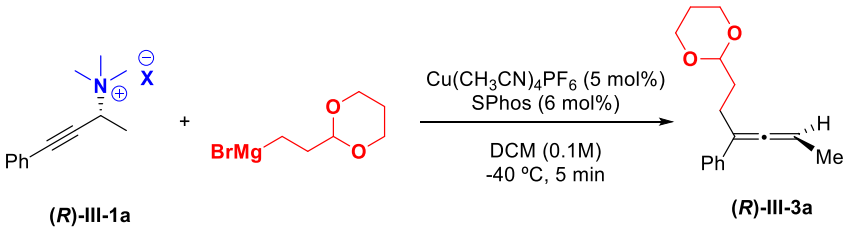
(*R*)-III-1a (*R*)-III-3a

Entry	T (ºC)	Yield[a] (%)	e.r.[b]
1	-40	92	98:2
2	0	70	95:5
3	rt	77	94:6

Reaction condition: **(*R*)-III-1a** (0.2 mmol, 1.0 equiv), AlkylMgX (1.1 equiv), $Cu(CH_3CN)_4PF_6$ (5 mol%), SPhos (6 mol%), CH_2Cl_2 (0.1 M), 5 min, unless otherwise noted. [a]Isolated yield after column chromatography. [b]Determined by chiral SFC.

We next explored the influence of the counteranion in the outcome of the transformation (**Table *3-7***). Switching from triflate to mesylate the yield and the enantiomeric excess dropped significantly (**Table *3-7***, entry 2). The use of tetrafluoroborate, iodine or tosylate afforded similar results as those observed with the mesylate (**Table *3-7***, entries 3-5).

Table 3-7: Influence of the nature of the counterion.



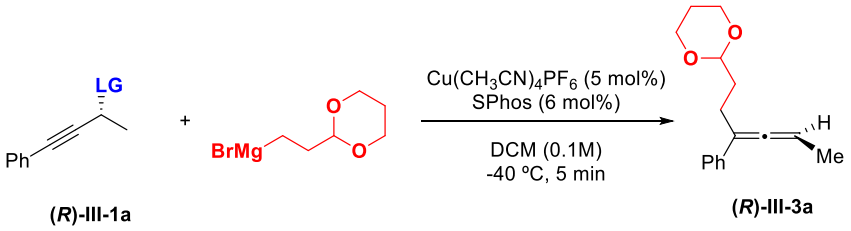
(*R*)-III-1a **(*R*)-III-3a**

Entry	X	Yield (%)[a]	e.r.[b]
1	**OTf**	92	98:2
2	**OMs**	57	71:29
3	**BF_4**	63	66:34
4	**I**	51	88:12
5	**OTs**	51	65:35

Reaction condition: **(*R*)-III-1a** (0.2 mmol, 1.0 equiv), AlkylMgX (1.1 equiv), $Cu(CH_3CN)_4PF_6$ (5 mol%), SPhos (6 mol%), CH_2Cl_2 (0.1 M), 5 min, unless otherwise noted. [a]Isolated yield after column chromatography. [b]Determined by chiral SFC.

We next checked if the nature of the leaving group had any influence in the reaction (**Table *3-8*Table *3-4***). We tried the reaction with the mesylate derivative, and we observed lower yield and some erosion of the stereospecificity (**Table *3-8***, entry 2).

Table 3-8: Influence of the leaving group.

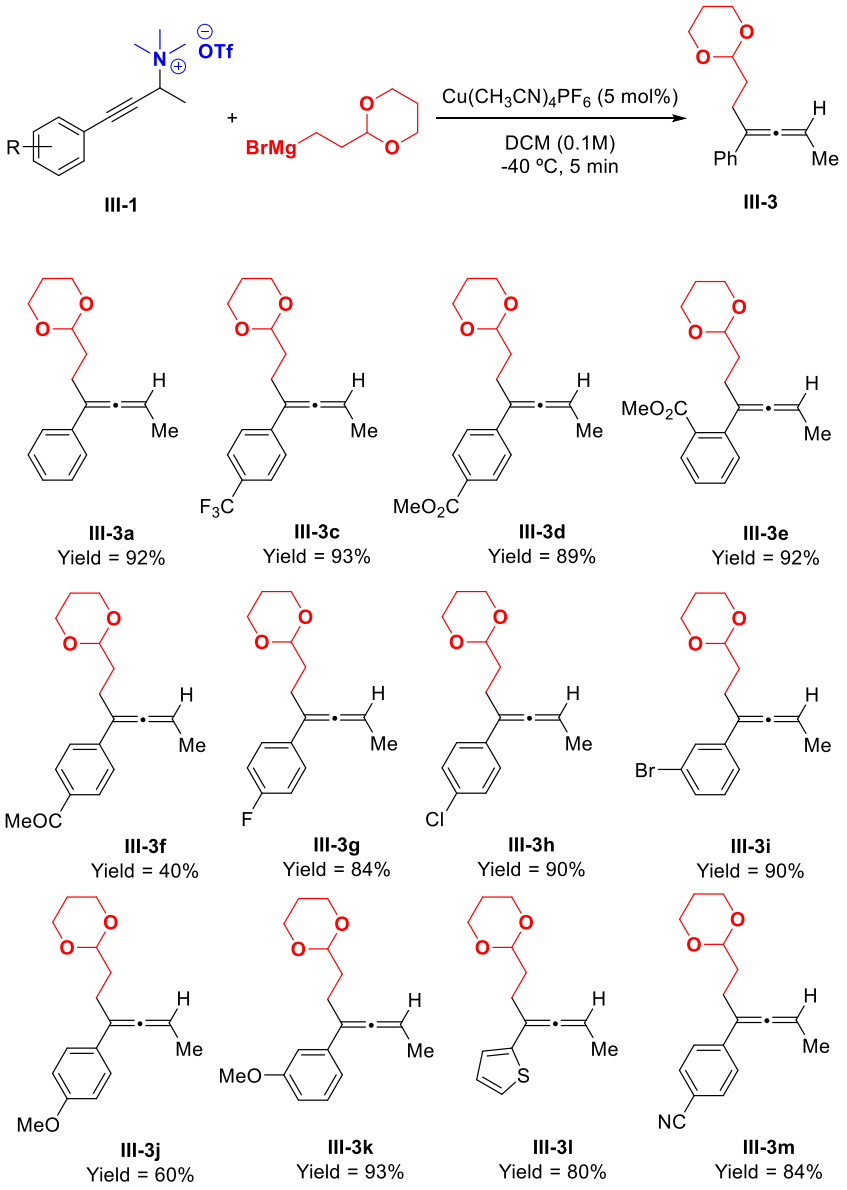


Entry	X	Yield (%)[a]	e.r.[b]
1	**NMe_3OTf**	**92**	**98:2**
2	**OMs**	55	87:13

Reaction conditions: **(*R*)-III-1a** (0.2 mmol, 1.0 equiv), AlkylMgX (1.1 equiv), $Cu(CH_3CN)_4PF_6$ (5 mol%), SPhos (6 mol%), CH_2Cl_2 (0.1 M), 5 min, unless otherwise noted. [a]Isolated yield after column chromatography. [b]Determined by chiral SFC.

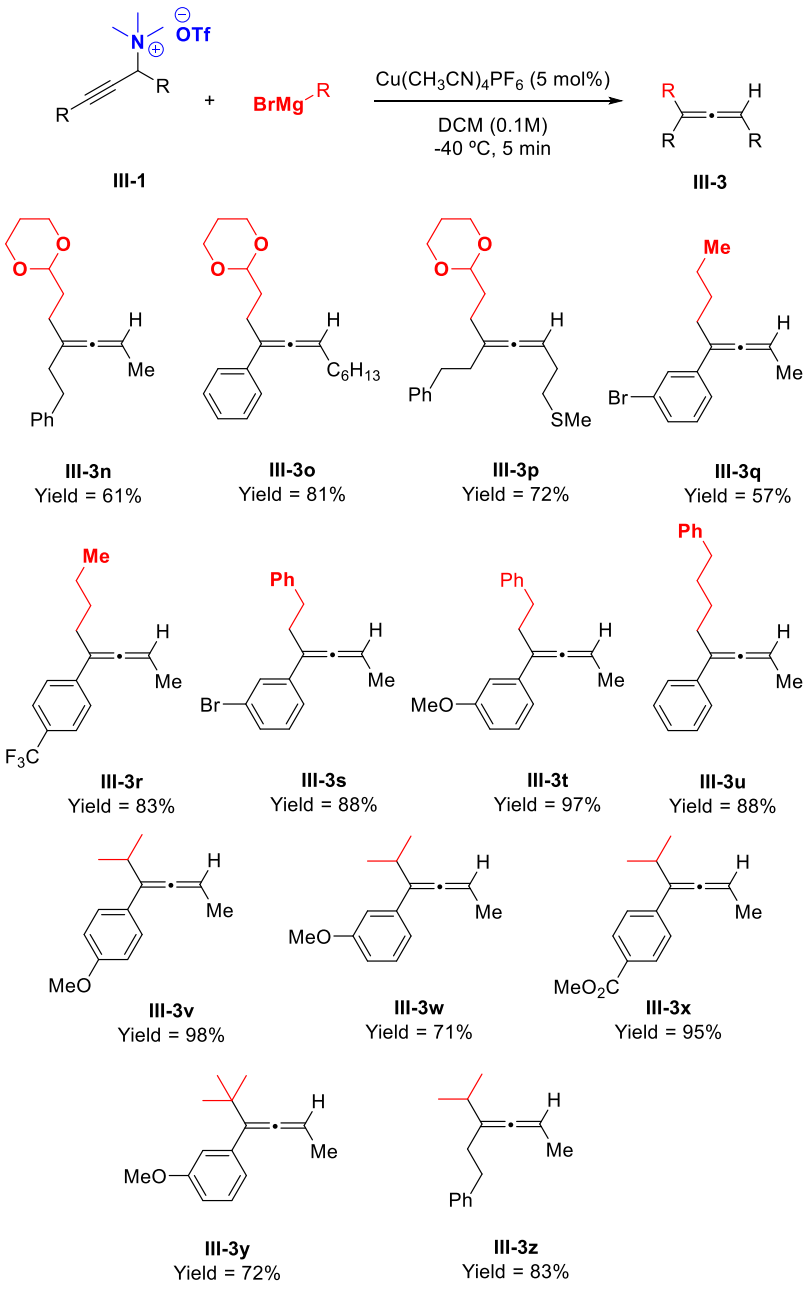
3.3.3. Scope of the Reaction.

With the optimal conditions in hand, we first proceeded to study the scope of the transformation with a series of racemic propargylic ammonium salts. We chose starting materials with different substituents on the alkyne and at the propargylic position (**Scheme *3-49*** and **Scheme *3-50***). In some cases, we observed low solubility of the ammonium salt in THF, therefore, we decided to carry out the study using CH_2Cl_2 as solvent. Using (1,3-dioxan-2-ylethyl)magnesium bromide, we prepared a broad range of trisubstituted allenes (compounds **III-3a-p**). The reaction worked well with aromatic substituents bearing electron withdrawing groups (**III-3c-f**). The fact that the reaction last only for five minutes allowed us to use esters (**III-3d-e**) and a ketone (**III-3f**) as substituent. This groups are not usually compatible with the use of Grignard reagents. With the more reactive ketone group, we observed formation of the product in 40% yield (compound **III-3f**) due to lower chemoselectivity. Aromatic substituent with halides (**III-3g-i**) reacted only through the C–N bond giving excellent results. We further modified the substitution on the alkyne with a thiophene ring (compound **III-3l**) with excellent results.



Scheme 3-49: Scope of the S_N2' substitution of propargylic ammonium salts.

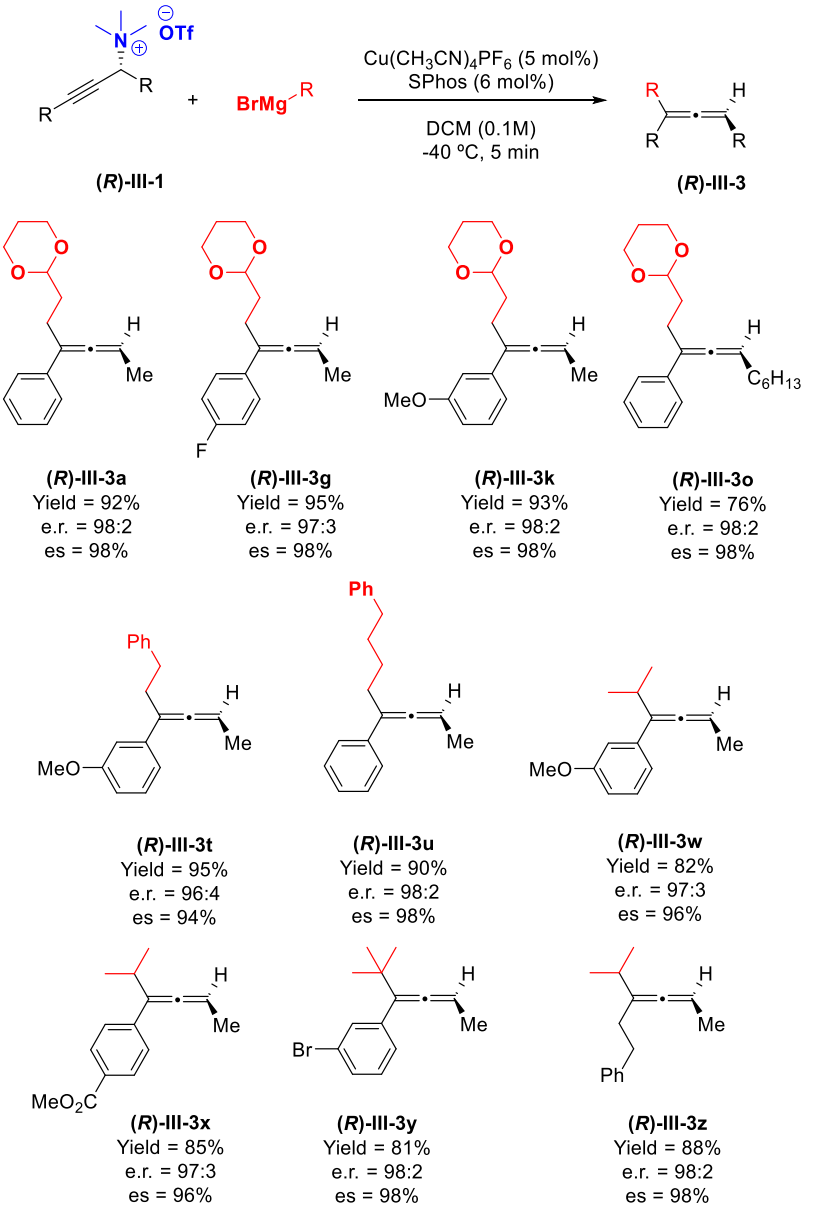
Alkyl chain on the alkyne also worked with good results (compounds **III-3n**). We also modified the propargylic position introducing alkyl chains other than methyl (compounds **III-3o** and **III-3p**). The use of different primary alkyl Grignard reagents gave the corresponding allenes with good yields (compounds **III-3q-u**). We also used secondary alkyl Grignard reagent with different substitution on the alkyne (compounds **III-3v-x** and **III-3z**). Even the use of *tert*-butylmagnesium bromide was compatible with the reaction conditions (compound **III-3y**). Unfortunately, silyl substituted alkynes did not react under the optimized conditions.



Scheme 3-50: Scope of the S_N2' substitution of propargylic ammonium salts.

3.3.4. Stereospecific Substitution.

During the optimization of the reaction conditions, we observed complete stereospecificity for compound **(*R*)-III-3a**. Therefore, the next step was to check if the chirality transfer was general for different ammonium salts and alkyl Grignard reagents. Ammonium salts with different aryl substitution such as fluorine (**(*R*)-III-3g**) or a methoxy group (**(*R*)-III-3k**) gave the desired product using (1,3-dioxan-2-ylethyl) magnesium bromide with excellent results. Compound **(*R*)-III-3o**, with a six-carbon chain on the propargylic position, was obtained also with excellent results. Changing the Grignard reagent to a different primary magnesium bromide (compounds **(*R*)-III-3t** and **(*R*)-III-3u**) did not affect the obtained results. The use of secondary (**(*R*)-III-3w-x** and **(*R*)-III-3z**) and even tertiary Grignard reagents (**(*R*)-III-3y**) was compatible with the reaction conditions with different substitution on the aromatic ring.

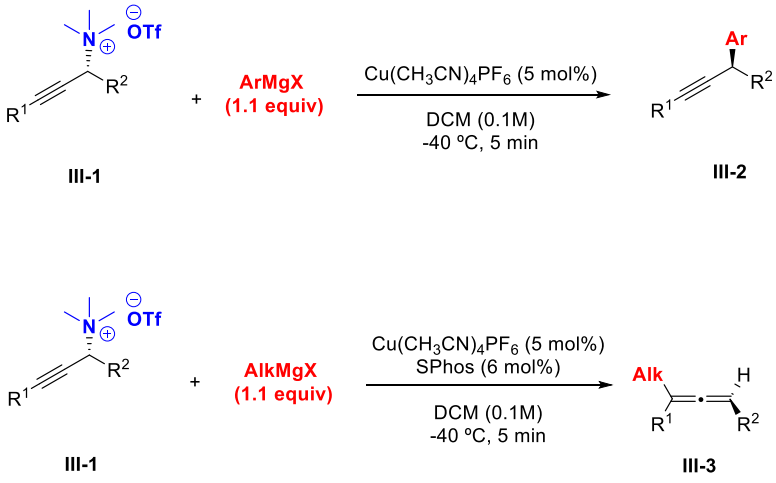


Scheme 3-51: Scope for the stereospecific S_N2' substitution of propargylic ammonium salts.

3.4. Conclusions.

In this chapter we have described the regioselective and stereospecific copper-catalyzed Kumada cross-coupling of propargylic ammonium salts with Grignard reagents. Our method represents the first stereospecific copper-catalyzed cross-coupling of propargylic substrates (**Scheme *3-52***). We could control the regioselectivity of the reaction by the nature of the Grignard reagent. Aryl magnesium halides formed exclusively the α-regioisomer whereas alkyl magnesium halides formed the allene with complete regioselectivity.

A combination of a commercially available, stable and inexpensive copper-salt and a simple phosphine in the case of alkyl Grignard reagents provided the enantiomerically enriched propargylic compounds or the allenes in high yield and almost perfect stereospecificity.

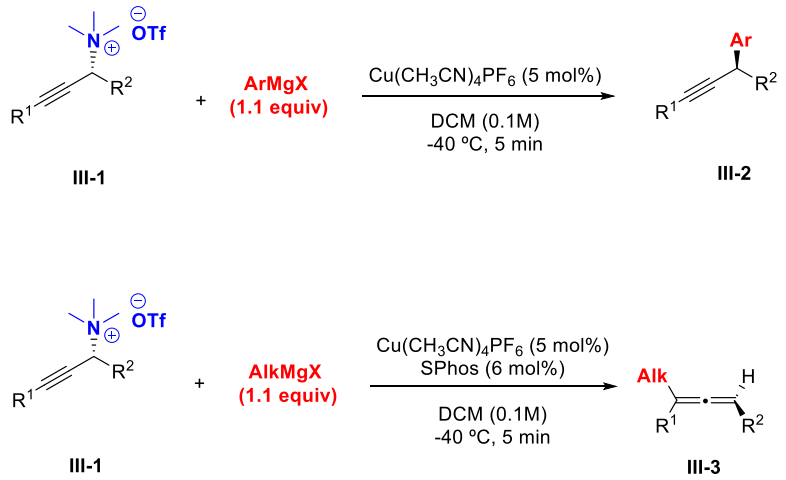


Scheme 3-52: Copper-catalyzed Kumada cross-coupling of propargylic ammonium salts.

3.5. Conclusiones.

En este capítulo, hemos descrito la reacción de acoplamiento cruzado de tipo Kumada catalizada por cobre entre sales de amonio propargílicas y reactivos de Grignard de manera regioselectiva y estereoespecífica. Esta metodologia representa la primera reacción de acoplamiento cruzado estereoespecífica y catalizada por cobre de sustratos propargílicos (**Esquema *3-53***). La regioselectividad de la reacción está controlada por la naturaleza de reactivo de Grignard. Haluros de arilmagnesio forman exclusivamente el regioisomero α, mientras que los haluros de alkilmagnesio forman el correspondiente aleno de manera totalmente regioselectiva.

Utilizando un catalizador comercial de cobre(I), y una fosfina en el caso de los haluros de alkilmagnesio, la reacción da lugar a compuestos propargílicos o alenos enantioméricamente enriquecidos con buenos rendimientos y una estereoespecificidad prácticamente total.



Esquema 3-53: Reacción de acoplamiento cruzado de tipo Kumada catalizado por cobre de sales de amonio propargílicas.

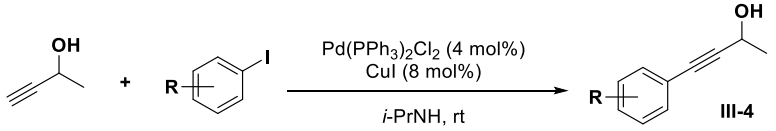
3.6. Supplementary Data.

Tetrahydrofuran and dichloromethane were purified by passing through a Pure Solv™ column drying system from Innovative Technology, Inc. Additionally, tetrahydrofuran and dichloromethane were degassed passing argon through them for 15 min. Diethyl ether was dried using activated 4Å molecular sieves and stored under argon. Unless indicated otherwise, all reactions were conducted under an argon atmosphere using flame-dried glassware with standard vacuum-line techniques. NMR spectra were acquired on a Bruker 300 spectrometer, running at 300, and 75 MHz for ^{1}H and ^{13}C NMR respectively. Chemical shifts (δ) are reported in ppm relative to residual solvent signals ($CDCl_3$, 7.26 ppm for ^{1}H NMR and 77.2 ppm for ^{13}C NMR respectively). ^{13}C NMR spectra were acquired on a broad band decoupled mode. The following abbreviations are used to describe peak patterns when appropriate: s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), sex (sextet), sept (septuplet), m (multiplet), br (broad). Analytical thin layer chromatography (TLC) was performed using pre-coated aluminum-backed plates (Merck Kieselgel 60 F254) and visualized by ultraviolet irradiation or phosphomolybdic acid dip or potassium permanganate dip. Purification of reaction mixtures was carried out by flash chromatography (FC) using silica gel Merck-60. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. The enantiomeric ratio (e.r.) of the products was determined by stationary phase SFC, HPLC or GC using chiral columns. Mass Spectrometry (MS) and High Resolution Mass Spectrometry (HRMS) were registered in a spectrometer GCT Agilent Technologies 6890N using Electronic Impact (E.I.) techniques at 70 eV, Fast Atom Bombardment and electrospray (ESI^+ or ESI^-). 4-(Trimethylsilyl)-3-butyn-2-ol, 3-phenyl-2-propyn-1-ol, 1-dimethylamino-3-(trimethylsilyl)-2-propyne were acquired from commercial sources.

Grignard reagents were acquired from commercial sources and were titrated prior to use.[79]

3.6.1. Synthesis of starting materials.

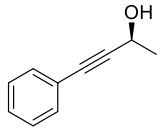
*3.6.1.1. Synthesis of propargylic alcohols, **III-4**.*



To an oven-dried round bottom flask was added the corresponding aryl iodine (1.2 equiv), $Pd(PPh_3)_2Cl_2$ (0.04 equiv) and copper(I) iodine (0.08 equiv). The flask was connected to an argon-vacuum line, evacuated and backfilled with argon (x3). Diisopropylamine (2.8 mL/mmol alcohol) was added and the reaction mixture was stirred at 0 ºC for 5 min. 3-Butyn-2-ol (1 equiv) was added dropwise at 0 ºC and the reaction mixture was stirred for 16 h at room temperature. Silica gel was added to the mixture and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography using the appropriate mixture of solvents.

[79] Krasovskiy, A.; Knochel, P. *Synthesis-Stuttgart*, **2006**, *5*, 890-891.

(–)-(*S*)-4-Phenylbut-3-yn-2-ol, **(*S*)-III-4a**.

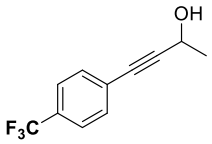


(*S*)-III-4a

From (*S*)-3-butyn-2-ol (0.50 g, 7.2 mmol), following the general procedure described above, compound **(*S*)-III-4a** (0.97 g, 6.6 mmol) was obtained in 92% yield as an orange oil after flash column chromatography (Cy/EtOAc, 95/5).

Compound **(*S*)-III-4a** was obtained in 99:1 enantiomeric ratio determined by SFC using Chiralpak-ID column [CO_2/MeOH (95:5)], 1.0 mL/min, τ_{major}= 15.7 min, τ_{minor}= 10.5 min. ^{1}H NMR, ^{13}C NMR and MS data were consistent with literature values.[80] **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.48 – 7.37 (m, 2H), 7.37 – 7.28 (m, 3H), 4.77 (m, 1H), 1.90 (d, *J* = 5.3 Hz, 1H), 1.56 (d, *J* = 6.6 Hz, 3H). **[α]$^{20}_D$**= –33.6 (*c* = 1.0, $CHCl_3$).

(±)-4-(4-(Trifluoromethyl)phenyl)but-3-yn-2-ol, **III-4c**.



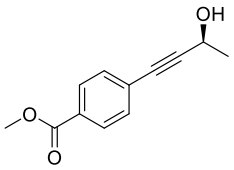
III-4c

From 3-butyn-2-ol (0.50 g, 7.2 mmol), following the general procedure described above, compound **III-4c** (1.34 g, 6.3 mmol) was obtained in 87% yield as an orange oil after flash column chromatography (Cy/EtOAc, 90/10).

^{1}H NMR, ^{13}C NMR and MS data were consistent with literature values.[81] **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.56 (m, 4H), 4.79 (q, *J* = 6.6 Hz, 1H), 1.89 (s, 1H), 1.58 (d, *J* = 6.6 Hz, 3H).

[80] Zhang, X., Lu, Z., Fu, C., Ma, S. *Org. Biomol. Chem.* **2009**, *7*, 3258-3263.
[81] Shatskiy, A., Kivijärvi, T., Lundberg, H., Tinnis, H., Adolfsson, H. *ChemCatChem*, **2015**, *7*, 3818-3821.

(–)-Methyl (*S*)-4-(3-hydroxybut-1-yn-1-yl)benzoate, **(*S*)-III-4d**.

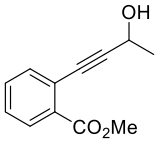


(*S*)-III-4d

From (*S*)-3-butyn-2-ol (0.50 g, 7.2 mmol), following the general procedure described above, compound **(*S*)-III-4d** (1.09 g, 5.3 mmol) was obtained in 74% yield as an orange oil after flash column chromatography (Cy/EtOAc, 90/10).

Compound **(*S*)-III-4d** was obtained in 99:1 enantiomeric ratio determined by SFC using Chiralpak-ID column [CO_2/MeOH (95:5)], 1.0 mL/min, τ_{major}= 20.3 min, τ_{minor}= 19.8 min. ^{1}H NMR, ^{13}C NMR and MS data were consistent with literature values.[82] **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.97 (d, *J* = 8.6 Hz, 2H), 7.47 (d, *J* = 8.6 Hz, 2H), 4.84 – 4.70 (m, 1H), 3.91 (s, 3H), 1.99 (d, *J* = 5.4 Hz, 1H), 1.56 (d, *J* = 6.6 Hz, 3H). **$[\alpha]^{20}_D$**= –28.2 (*c* = 1.0, $CHCl_3$).

(±)-Methyl 2-(3-hydroxybut-1-yn-1-yl)benzoate, **III-4e**.



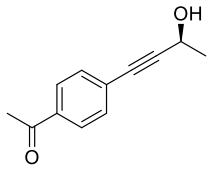
III-4e

From 3-butyn-2-ol (0.50 g, 7.2 mmol), following the general procedure described above, compound **III-4e** (1.04 g, 5.1 mmol) was obtained in 71% yield as an orange oil after flash column chromatography (Cy/EtOAc, 90/10).

^{1}H NMR, ^{13}C NMR and MS data were consistent with literature values.[83] **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.94 (d, *J* = 7.7 Hz, 1H), 7.54 (d, *J* = 6.6 Hz, 1H), 7.47 (td, *J* = 7.5, 1.3 Hz, 1H), 7.37 (td, *J* = 7.6, 1.3 Hz, 1H), 4.82 (q, *J* = 6.6 Hz, 1H), 3.93 (s, 3H), 2.48 (s, 1H), 1.59 (d, *J* = 6.6 Hz, 3H).

[82] Harris, R. J., Nakafuku, K., Widenhoefer, R. A. *Chem. Euro. J.*, **2014**, *20*, 12245-12254.
[83] Gangadhararao, G.; Kotikalapudi, R.; Reddy, M. N.; Swamy, K. C. K. *Beilstein J. Org. Chem.* **2014**, *10*, 996-1005.

(−)-(*S*)-1-[4-(3-Hydroxybut-1-yn-1-yl)phenyl]ethan-1-one, **(*S*)-III-4f**.

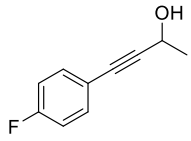


(*S*)-III-4f

From (*S*)-3-butyn-2-ol (0.50 g, 7.2 mmol), following the general procedure described above, compound **(*S*)-III-4f** (1.22 g, 6.5 mmol) was obtained in 90% yield as an orange oil after flash column chromatography (Cy/EtOAc 90/10).

Compound **(*S*)-III-4f** was obtained in 99:1 enantiomeric ratio determined by SFC using Chiralpak-ID column [CO_2/MeOH (95:5)], 1.0 mL/min, τ_{major}= 24.9 min, τ_{minor}= 23.5 min. ^{1}H NMR, ^{13}C NMR and MS data were consistent with literature values.[84] **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.90 (d, *J* = 8.5 Hz, 2H), 7.50 (d, *J* = 8.5 Hz, 2H), 4.85 – 4.71 (m, 1H), 2.60 (s, 3H), 1.97 (d, *J* = 5.4 Hz, 1H), 1.57 (d, *J* = 6.6 Hz, 3H). **[α]$^{20}_D$**= –32.4 (*c* = 1.0, $CHCl_3$).

(±)-4-(4-Fluorophenyl)but-3-yn-2-ol, **III-4g**.



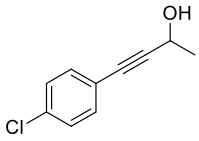
III-4g

From 3-butyn-2-ol (0.89 g, 12.7 mmol), following the general procedure described above, compound **III-4g** (1.8 g, 10.9 mmol) was obtained in 86% yield as an orange oil after flash column chromatography using (Cy/EtOAc, 90/10).

^{1}H NMR, ^{13}C NMR and MS data were consistent with literature values.[85] **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.51 – 7.32 (m, 2H), 7.07 – 6.94 (m, 2H), 4.84 – 4.64 (m, 1H), 2.12 (s, 1H), 1.56 (d, *J* = 6.6 Hz, 3H).

[84] Dutta, P.; Sarkar, A. *Adv. Synth. Catal.* **2011**, *353*, 2814-2822.
[85] Wang, Q., Kobayashi, Y. *Tetrahedron Lett.*, **2010**, *51*, 5592-5595.

(±)-4-(4-Chlorophenyl)but-3-yn-2-ol, **III-4h**.

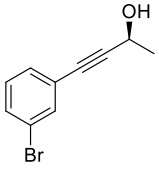


III-4h

From 3-butyn-2-ol (0.50 g, 7.2 mmol), following the general procedure described above, compound **III-4h** (1.24 g, 6.8 mmol) was obtained in 95% yield as an orange oil after flash column chromatography using (Cy/EtOAc, 90/10).

^{1}H NMR, ^{13}C NMR and MS data were consistent with literature values.[80] **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.37 (d, *J* = 8.6 Hz, 2H), 7.29 (d, *J* = 8.7 Hz, 2H), 4.76 (q, *J* = 6.6 Hz, 1H), 1.91 (s, 1H), 1.56 (d, *J* = 6.6 Hz, 3H).

(–)-(*S*)-4-(3-Bromophenyl)but-3-yn-2-ol, **(*S*)-III-4i**.



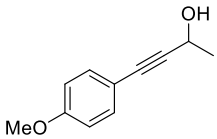
(*S*)-III-4i

From (*S*)-3-butyn-2-ol (0.50 g, 7.2 mmol), following the general procedure described above, compound **(*S*)-III-4i** (1.34 g, 6.0 mmol) was obtained in 83% yield as an orange oil after flash column chromatography using (Cy/EtOAc, 90/10).

Compound **(*S*)-III-4i** was obtained in 99:1 enantiomeric ratio determined by SFC using Chiralpak-IB column [CO_2/MeOH (95:5)], 1.0 mL/min, τ_{major}= 17.3 min, τ_{minor}= 14.2 min. ^{1}H NMR, ^{13}C NMR and MS data were consistent with literature values.[86] **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.59 (s, 1H), 7.46 (d, *J* = 8.0 Hz, 1H), 7.36 (d, *J* = 7.7 Hz, 1H), 7.19 (t, *J* = 7.9 Hz, 1H), 4.76 (q, *J* = 6.6 Hz, 1H), 1.89 (s, 1H), 1.56 (d, *J* = 6.6 Hz, 3H). **$[\alpha]^{20}_{D}$**= –22.7 (*c* = 1.0, $CHCl_3$).

[86] Schubert, T., Hummel, W., Kula, M., Müller, M. *Eur. J. Org. Chem.* **2001**, *22*, 4181-4187.

(±)-4-(4-Methoxyphenyl)but-3-yn-2-ol, **III-4j**.

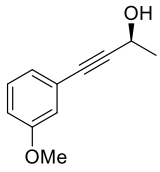


III-4j

From 3-butyn-2-ol (0.50 g, 7.2 mmol), following the general procedure described above, compound **III-4j** (0.78 g, 4.4 mmol) was obtained in 62% yield as an orange oil after flash column chromatography using (Cy/EtOAc, 90/10).

^{1}H NMR, ^{13}C NMR and MS data were consistent with literature values.[87] **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.36 (d, *J* = 8.9 Hz, 2H), 6.83 (d, *J* = 8.9 Hz, 2H), 4.81 – 4.65 (m, 1H), 3.81 (s, 3H), 1.87 (d, *J* = 5.3 Hz, 1H), 1.54 (d, *J* = 6.6 Hz, 3H).

(–)-(*S*)-4-(3-Methoxyphenyl)but-3-yn-2-ol, **(*S*)-III-4k**.



(*S*)-III-4k

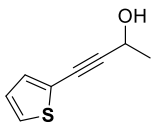
From (*S*)-3-butyn-2-ol (0.50 g, 7.2 mmol), following the general procedure described above, compound **(*S*)-III-4k** (1.08 g, 6.1 mmol) was obtained in 84% yield as an orange oil after flash column chromatography using (Cy/EtOAc, 90/10).

Compound **(*S*)-III-4k** was obtained in 99:1 enantiomeric ratio determined by SFC using Chiralpak-IB column [CO_2/MeOH (95:5)], 1.0 mL/min, τ_{major}= 20.4 min, τ_{minor}= 13.3 min. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.21 (t, *J* = 8.0 Hz, 1H), 7.02 (dt, *J* = 7.6, 1.1 Hz, 1H), 6.96 (m, 1H), 6.87 (ddd, *J* = 8.0, 2.6, 1.1 Hz, 1H), 4.83–4.68 (m, 1H), 3.79 (s, 3H), 2.00 (d, *J* = 5.1 Hz, 1H), 1.55 (d, *J* = 6.6 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 159.3, 129.4, 124.3, 123.7, 116.5, 115.0, 91.0, 83.9, 58.8, 55.3, 24.4.

[87] Saravanan, T.; Jana, S.; Chadha, A. *Org. Biomol. Chem*, **2014**, *12*, 4682-4690.

[α]$^{20}_{D}$= –26.5 (*c* = 1.0, $CHCl_3$). **HRMS-ESI$^+$** m/z calculated for $C_{11}H_{12}O_2Na$ $[M+Na]^+$:199.0729, found 199.0732.

(±)-4-(Thiophen-2-yl)but-3-yn-2-ol, **III-4l**.

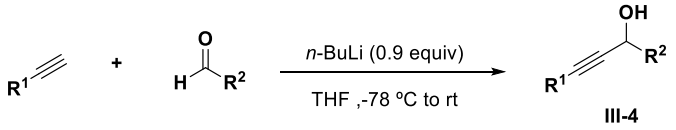


III-4l

From 3-butyn-2-ol (0.50 g, 7.2 mmol), following the general procedure described above, compound **III-4l** (0.75 g, 4.9 mmol) was obtained in 68% yield as an orange oil after flash column chromatography using (Cy/EtOAc, 90/10).

^{1}H NMR, ^{13}C NMR and MS data were consistent with literature values.[88] **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.27 (d, *J* = 5.4 Hz, 1H), 7.21 (d, *J* = 3.4 Hz, 1H), 7.04 – 6.91 (m, 1H), 4.78 (d, *J* = 4.8 Hz, 1H), 1.96 (s, 1H), 1.56 (d, *J* = 6.6 Hz, 3H).

*3.6.1.2. Synthesis of alcohols **III-4n**, **III-4o**, **III-4p** and **III-4w**.*

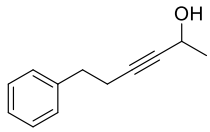


III-4

To a solution of the corresponding acetylene (1 equiv) in THF (0.7M) at -78 °C was added *n*-butyllithium (2.5M in hexane, 0.9 equiv). After stirring 30 min, the corresponding aldehyde (1.1 equiv) was added and the mixture was warmed to room temperature. Water was added to quench the reaction and the layers were separated. The aqueous phase was extracted with ether (3x) and the combined extracts were dried over magnesium sulfate. The solvent was evaporated under reduced pressure and the crude product was purified by flash column chromatography.

[88] Panteleev, J.; Huang, R. Y.; Lui, E. K. J.; Lautens, M. *Org. Lett.* **2011**, *13*, 5314-5317.

(±)-6-Phenylhex-3-yn-2-ol, **III-4n**.



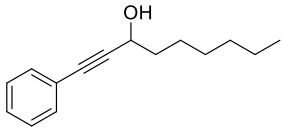
III-4n

From but-3-yn-1-ylbenzene (2.60 g, 20 mmol), following the general procedure described above, compound **III-4n** (2.51 g, 14.4 mmol) was obtained in 72% yield as a yellow oil after flash column chromatography using (Cy/EtOAc, 90/10).

^{1}H NMR, ^{13}C NMR and MS data were consistent with literature values.[89]

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 (m, 2H), 7.25 – 7.18 (m, 3H), 4.56 – 4.41 (m, 1H), 2.82 (t, *J* = 7.6 Hz, 2H), 2.49 (td, *J* = 7.5, 1.8 Hz, 2H), 1.68 (m, 1H), 1.41 (d, *J* = 6.5 Hz, 3H).

(±)-1-Phenylnon-1-yn-3-ol, **III-4o**.



III-4o

From phenylacetylene (3.72 g, 36 mmol), following the general procedure described above, compound **III-4o** (7.14 g, 33.1 mmol) was obtained in 92% yield as a yellow oil after flash column chromatography using (Cy/EtOAc, 90/10).

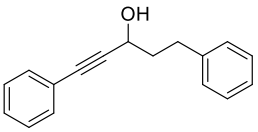
^{1}H NMR, ^{13}C NMR and MS data were consistent with literature values.[90]

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 – 7.37 (m, 2H), 7.31 (m, 3H), 4.60 (m, 1H), 1.86 (d, *J* = 5.6 Hz, 1H), 1.80 (m, 2H), 1.56 – 1.45 (m, 2H), 1.33 (m, 6H), 0.89 (t, *J* = 6.5 Hz, 3H).

[89] Jiang, B.; Chen, Z.; Xiong, W. *Chem. Comm.* **2002**, *14*, 1524-1525.

[90] Boussonniere, A.; Beneteau, R.; Zimmermann, N.; Lebreton, J.; Denes, F. *Chem. Eur. J.* **2011**, *17*, 5613-5627.

(±)-1,5-Diphenylpent-1-yn-3-ol, **III-4p**.



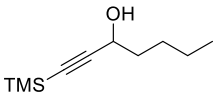
III-4p

From phenylacetylene (3.3 g, 30 mmol), following the general procedure described above, compound **III-4p** (5.32 g, 22.5 mmol) was obtained in 75% yield as a yellow oil after flash column chromatography using (Cy/EtOAc, 90/10).

^{1}H NMR, ^{13}C NMR and MS data were consistent with literature values.[91]

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 – 7.38 (m, 2H), 7.36 – 7.21 (m, 8H), 4.61 (q, 6.4 Hz, 1H), 2.95 – 2.79 (m, 2H), 2.21 – 2.03 (m, 2H), 1.94 – 1.84 (m, 1H).

(±)-1-(Trimethylsilyl)hept-1-yn-3-ol, **III-4w**.



III-4w

From trimethylsilylacetylene (4.91 g, 50 mmol), following the general procedure described above, compound **III-4w** (7.5 g, 40.5 mmol) was obtained in 81% yield as a yellow oil after flash column chromatography using (Cy/EtOAc, 90/10).

^{1}H NMR, ^{13}C NMR and MS data were consistent with literature values.[92]

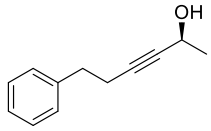
^{1}H NMR (300 MHz, $CDCl_3$) δ 4.35 (q, 6.5 Hz, 1H), 1.80 (d, J = 5.4 Hz, 1H), 1.74 – 1.64 (m, 2H), 1.40 (m, 4H), 0.91 (t, J = 7.1 Hz, 3H), 0.17 (s, 9H).

[91] Kapeller, D. C.; Kocienski, P. J. *Synthesis* **2010**, *22*, 3811-3821.
[92] Ivanov, I. V.; Romanov, S. G.; Groza, N. V.; Nigam, S.; Kuhn, H.; Myagkova, G. I. *Bioorgan. Med. Chem.* **2002**, 10, 2335-2343.

*3.6.1.3. Synthesis of enantiomerically enriched alcohol **(S)-III-4** through kinetic resolution.*

To an oven-dried round bottom flask was added **III-4** (1 equiv), molecular sieves (50% w/w) and Amano Lipase from Pseudomonas fluorescens (50 % w/w). The flask was connected to an argon-vacuum line, evacuated and backfilled with argon (x3). *n*-Hexane (6 mL/mmol of alcohol) was added to the mixture. After that, vinyl acetate (3 equiv) was added and the mixture was stirred at room temperature for 24 h. After completion (checked by chiral SFC) the reaction was filtered, and the solvent was removed under reduced pressure.

(–)-(*S*)-6-Phenylhex-3-yn-2-ol, **(*S*)-III-4n**.

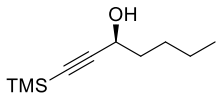


(*S*)-III-4n

From (±)-6-Phenylhex-3-yn-2-ol (1.9 g, 10.9 mmol), following the general procedure described above, compound **(*S*)-III-4n** (0.85 g, 4.9 mmol) was obtained in 45% yield as a yellow oil after flash column chromatography using (Cy/EtOAc, 90/10).

Compound **(*S*)-III-4n** was obtained in 99:1 enantiomeric ratio determined by HPLC using Chiralpak-IBN column [CO_2/MeOH (95:5)], 1.0 mL/min, τ_{major}= 11.2 min, τ_{minor}= 6.4 min. $[\alpha]^{20}_{D}$= –33.1 (*c* = 1.0, $CHCl_3$).

(–)-(*S*)-1-(trimethylsilyl)hept-1-yn-3-ol, **(*S*)-III-4w**.

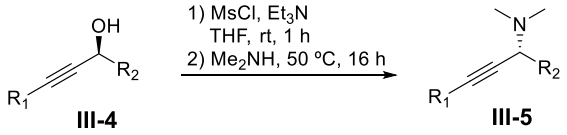


(*S*)-III-4w

From 1-(trimethylsilyl)hept-1-yn-3-ol (5.0 g, 27.1 mmol), following the general procedure described above, compound **(*S*)-III-4w** (2.3 g, 12.5 mmol) was obtained in 46% yield as a yellowish oil after flash column chromatography (Cy/EtOAc, 95/5). ^{1}H NMR, ^{13}C NMR and MS data were consistent with literature values.[92] $[\alpha]^{20}_{D}$= –6.2 (*c* = 1.0, $CHCl_3$).

Compound **(*S*)-III-4w** was transformed into **(*S*)-III-6w** through desilylation and benzoylation to determine the enantiomeric ratio (See compound **(*S*)-III-6w**).

*3.6.1.4. Synthesis of dimethylamines, **III-5**.*

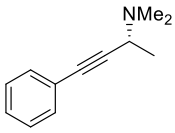


To a solution of the alcohol (1 equiv) and triethylamine (5 equiv) in THF (2.5 mL/mmol of alcohol) was added methanesulfonyl chloride (2 equiv) at 0 ºC. The reaction was stirred for 1h at room temperature and then, a solution of dimethylamine (2 M in THF, 5 equiv) was added to the mixture. The temperature was raised to 50 ºC and the reaction mixture was stirred for 16 h. The reaction mixture was filtered through a short pad of Celite® and rinsed with Et_2O. The solvent was removed under reduced pressure and the crude product was purified by flash column chromatography (From Cy/EtOAc 2:1 to EtOAc gradient).

The complete transfer of chirality in the S_N2 reaction was demonstrated for compound **(*R*)-III-5i** using chiral GC analysis (see below). The inversion of the stereochemistry in **(*R*)-III-5i** was proved for its ammonium salt derivative **(*R*)-III-1i**, through single crystal X-ray crystallography (see section **3.2.2**). For the other propargylic amines, we assumed complete chirality transfer and inversion of the stereochemistry in

the S_N2 reaction.[93] This assumption is supported by the high fidelity between the enantiomeric excess of the propargylic alcohol and the enantiomeric excess of the coupling products. This is only possible if the S_N2 reaction to form the dimethylamine takes place with complete chirality transfer.

(+)-(*R*)-*N*,*N*-Dimethyl-4-phenylbut-3-yn-2-amine, **(*R*)-III-5a**.

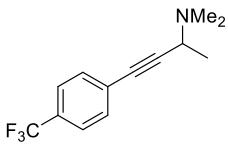


(*R*)-III-5a

From (*S*)-4-phenylbut-3-yn-2-ol (450 mg, 3 mmol), following the general procedure described above, compound **(*R*)-III-5a** (442 mg, 2.6 mmol) was obtained in 85% yield as an orange oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 – 7.39 (m, 2H), 7.33 – 7.25 (m, 3H), 3.69 (q, *J* = 7.0 Hz, 1H), 2.33 (s, 6H), 1.40 (d, *J* = 7.0 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 131.8, 128.3, 128.0, 123.5, 87.8, 85.3, 52.9, 41.4, 20.1. **$[\alpha]^{20}_D$**= +33.4 (*c* = 1.0, $CHCl_3$). **HRMS-ESI$^+$** m/z calculated for $C_{12}H_{16}N$ $[M+H]^+$: 174.1277, found 174.1275.

(±)-*N*,*N*-Dimethyl-4-[4-(trifluoromethyl)phenyl]but-3-yn-2-amine, **III-5c**.



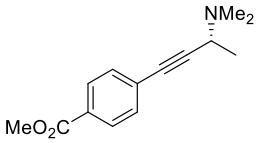
III-5c

From (±)-4-[4-(trifluoromethyl)phenyl]but-3-yn-2-ol (1.1 g, 5 mmol), following the general procedure described above, compound **III-5c** (1.1 g, 4.5 mmol) was obtained in 89% yield as an orange oil.

[93] For similar S_N2 reactions, see: (a) Davidson, M. H.; McDonald, F. E. *Org. Lett*. **2004**, *6*, 1601-1603. (b) Hanamoto, T.; Shimomoto, N.; Kikukawa, T.; Inanaga, J. *Tetrahedron: Asymmetry* **1999**, *10*, 2951-2959.

^{1}H NMR (300 MHz, $CDCl_3$) 7.66 – 7.40 (m, 4H), 3.71 (q, *J* = 7.0 Hz, 1H), 2.34 (s, 6H), 1.41 (d, *J* = 7.0 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 132.1, 129.9 (q, J_{C-F} = 32 Hz), 127.3 (q, J_{C-F} = 1.4 Hz), 125.3 (q, J_{C-F} = 3.9 Hz), 124.1 (q, J_{C-F} = 271.8 Hz), 90.7, 84.2, 52.9, 41.5, 19.9. **HRMS-EI$^+$** m/z calculated for $C_{13}H_{14}NF_3$ [M]$^+$: 241.1078, found 241.1068.

(+)-Methyl (*R*)-4-[3-(dimethylamino)but-1-yn-1-yl]benzoate, **(*R*)-III-5d**.

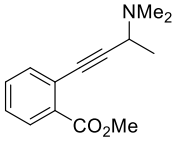


(*R*)-III-5d

From methyl (*S*)-4-(3-hydroxybut-1-yn-1-yl)benzoate (600 mg, 2.94 mmol), following the general procedure described above, compound **(*R*)-III-5d** (564.2 mg, 2.4 mmol) was obtained in 83% yield as an orange oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97 (d, *J* = 8.3 Hz, 2H), 7.48 (d, *J* = 8.3 Hz, 2H), 3.91 (s, 3H), 3.71 (q, *J* = 7.0 Hz, 1H), 2.33 (s, 6H), 1.41 (d, *J* = 7.0 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 166.5, 131.6, 129.4, 129.2, 128.1, 91.1, 84.7, 52.8, 52.2, 41.3, 19.8. **$[\alpha]^{20}_D$**= +38.1 (*c* = 1.0, $CHCl_3$). **HRMS-ESI$^+$** m/z calculated for $C_{14}H_{18}NO_2$ [M+H]$^+$: 232.1332, found 232.1324.

(±)-Methyl 2-[3-(dimethylamino)but-1-yn-1-yl]benzoate, **III-5e**.



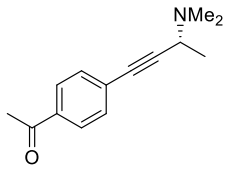
III-5e

From (±)-methyl 2-(3-hydroxybut-1-yn-1-yl)benzoate (816 mg, 4.0 mmol), following the general procedure described above, compound **III-5e** (693 mg, 3.0 mmol) was obtained in 75% yield as an orange oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.52 (dd, *J* = 7.7, 1.3 Hz, 1H), 7.40 (td, *J* = 7.6, 1.4 Hz, 1H), 7.30 (td, *J* = 7.6, 1.4 Hz,

1H), 3.88 (s, 3H), 3.73 (q, *J* = 7.0 Hz, 1H), 2.35 (s, 6H), 1.41 (d, *J* = 7.0 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 166.8, 134.4, 132.1, 131.4, 130.2, 127.5, 123.6, 93.3, 83.9, 53.0, 52.1, 41.3, 19.9. **HRMS-ESI$^+$** m/z calculated for $C_{14}H_{18}NO_2$ $[M+H]^+$: 232.1332, found 232.1327.

(+)-(*R*)-1-(4-(3-(Dimethylamino)but-1-yn-1-yl)phenyl)ethan-1-one, **(*R*)-III-5f**.

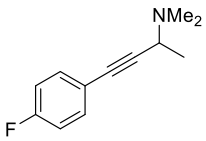


(*R*)-III-5f

From (*S*)-1-(4-(3-hydroxybut-1-yn-1-yl)phenyl)ethan-1-one (750 mg, 4 mmol), following the general procedure described above, compound **(*R*)-III-5f** (613 mg, 2.8 mmol) was obtained in 71% yield as an orange oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 (d, *J* = 8.5 Hz, 2H), 7.50 (d, *J* = 8.5 Hz, 2H), 3.71 (q, *J* = 7.0 Hz, 1H), 2.58 (s, 3H), 2.33 (s, 6H), 1.41 (d, *J* = 7.0 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 197.3, 136.0, 131.8, 128.3, 128.2, 91.5, 84.6, 52.8, 41.3, 26.5, 19.7. **$[\alpha]^{20}_D$**= +35.5 (*c* = 1.0, $CHCl_3$). **HRMS-ESI$^+$** m/z calculated for $C_{14}H_{18}NO$ $[M+H]^+$: 216.1382, found 216.1384.

(±)-4-(4-Fluorophenyl)-*N*,*N*-dimethylbut-3-yn-2-amine, **III-5g**.

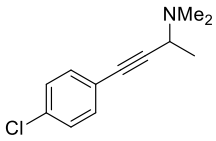


III-5g

From (±)-4-(4-fluorophenyl)but-3-yn-2-ol (1.0 g, 6.1 mmol), following the general procedure described above, compound **III-5g** (959 mg, 5.0 mmol) was obtained in 82% yield as an orange oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 – 7.34 (m, 2H), 6.97 (t, *J* = 8.8 Hz, 2H), 3.65 (q, *J* = 7.0 Hz, 1H), 2.31 (s, 6H), 1.38 (d, *J* = 7.0 Hz, 3H).**^{13}C NMR** (75 MHz, $CDCl_3$) δ 162.3 (d, J_{C-F} = 249 Hz), 133.0 (d, J_{C-F} = 8.25 Hz), 119.4 (d, J_{C-F} = 3.75 Hz), 115.4 (d, J_{C-F} = 22.5 Hz), 87.4 (d, J_{C-F} = 1.5 Hz), 84.1, 52.7, 41.3, 19.9. **HRMS-ESI^{+}** m/z calculated for $C_{12}H_{15}NF$ $[M+H]^{+}$: 192.1183, found 192.1184.

(±)-4-(4-Chlorophenyl)-*N*,*N*-dimethylbut-3-yn-2-amine, **III-5h.**

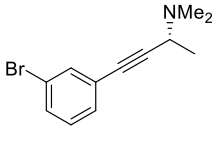


III-5h

From (±)-4-(4-chlorophenyl)but-3-yn-2-ol (1.08 g, 6.0 mmol), following the general procedure described above, compound **III-5h** (976 mg, 4.7 mmol) was obtained in 78% yield as an orange oil.

^{1}H NMR (300 MHz, $CDCl_3$) 7.30 (d, *J* = 8.6 Hz, 2H), 7.20 (d, *J* = 8.6 Hz, 2H), 3.63 (q, *J* = 7.0 Hz, 1H), 2.27 (s, 6H), 1.35 (d, *J* = 7.0 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 133.8, 132.8, 128.4, 121.8, 88.7, 84.1, 52.7, 41.1, 19.8. **HRMS-EI^{+}** m/z calculated for $C_{12}H_{14}NCl$ $[M]^{+}$: 207.0815, found 207.0810.

(+)-(*R*)-4-(3-Bromophenyl)-*N*,*N*-dimethylbut-3-yn-2-amine, **(*R*)-III-5i.**



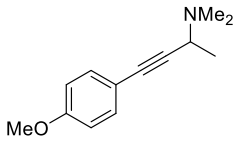
(*R*)-III-5i

From (*S*)-4-(3-bromophenyl)but-3-yn-2-ol (1.24 g, 5.5 mmol), following the general procedure described above, compound **(*R*)-III-5i** (1.26 g, 5.0 mmol) was obtained in 91% yield as an orange oil.

Compound **(*R*)-III-5i** was obtained in 99:1 enantiomeric ratio determined by GC on a Chirasil Dex-CB column (160 °C, hold 2 min, then →170 °C @ 0.3 °C/min, hold 5 min; then →180 °C @ 5 °C/min, hold 5 min flow rate 1.0 mL/min.). τ_{major}= 8.3 min, τ_{minor}= 8.1 min. **^{1}H NMR** (300

MHz, $CDCl_3$) 7.58 (m, 1H), 7.43 (d, *J* = 7.9 Hz, 1H), 7.35 (d, *J* = 7.9 Hz, 1H), 7.16 (t, *J* = 7.9 Hz, 1H), 3.69 (q, *J* = 7.0 Hz, 1H), 2.32 (s, 6H), 1.39 (d, *J* = 7.0 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 134.7, 131.2, 130.4, 129.8, 125.5, 122.2, 89.5, 84.0, 52.9, 41.5, 20.0. **$[\alpha]^{20}_D$**= +35.2 (*c* = 1.0, $CHCl_3$). **HRMS-EI$^+$** m/z calculated for $C_{12}H_{14}NBr[M]^+$: 251.0310, found 251.0298.

(±)-4-(4-Methoxyphenyl)-*N*,*N*-dimethylbut-3-yn-2-amine, **III-5j**.

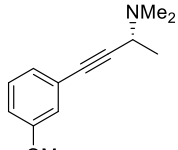


III-5j

From (±)-4-(4-methoxyphenyl)but-3-yn-2-ol (790 mg, 4.5 mmol), following the general procedure described above, compound **III-5j** (608 mg, 3.0 mmol) was obtained in 67% yield as an orange oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 (d, *J* = 8.9 Hz, 2H), 6.82 (d, *J* = 8.9 Hz, 2H), 3.80 (s, 3H), 3.67 (q, *J* = 7.0 Hz, 1H), 2.32 (s, 6H), 1.39 (d, *J* = 7.0 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 159.5, 133.2, 115.6, 114.0, 86.2, 85.1, 55.4, 52.9, 41.4, 20.2. **HRMS-ESI$^+$** m/z calculated for $C_{13}H_{18}NO$ $[M+H]^+$: 204.1382, found 204.1383.

(+)-*(R)*-4-(3-Methoxyphenyl)-*N*,*N*-dimethylbut-3-yn-2-amine, **(*R*)-III-5k.**



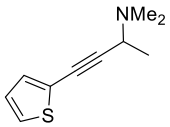
(*R*)-III-5k

From (*S*)-4-(3-methoxyphenyl)but-3-yn-2-ol (900 mg, 5.1 mmol), following the general procedure described above, compound **(*R*)-III-5k** (842 mg, 4.4 mmol) was obtained in 87% yield as an orange oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.19 (t, *J* = 7.9 Hz, 1H), 7.02 (dt, *J* = 7.6, 1.2 Hz, 1H), 6.95 (m, 1H), 6.85 (dd, *J* = 8.3, 2.0 Hz, 1H), 3.79 (s, 3H), 3.68 (q, *J* = 7.0 Hz, 1H), 2.33 (s, 6H), 1.40 (d, *J* = 7.0 Hz, 3H). **^{13}C NMR** (75

MHz, $CDCl_3$) δ 159.4, 129.4, 124.4 (2C), 116.7, 114.5, 87.7, 85.2, 55.3, 52.8, 41.4, 20.1. **$[\alpha]^{20}_D$**= +35.9 (*c* = 1.0, $CHCl_3$). **HRMS-ESI$^+$** m/z calculated for $C_{13}H_{18}NO$ $[M+H]^+$: 204.1382, found 204.1382.

(±)-*N*,*N*-Dimethyl-4-(thiophen-2-yl)but-3-yn-2-amine, **III-5l**.

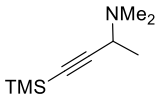


III-5l

From (±)-4-(thiophen-2-yl)but-3-yn-2-ol (970 g, 6.4 mmol), following the general procedure described above, compound **III-5l** (660 g, 3.7 mmol) was obtained in 58% yield as an orange oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.18 – 7.12 (m, 2H), 6.91 (m, 1H), 3.67 (q, *J* = 7.0 Hz, 1H), 2.29 (s, 6H), 1.36 (d, *J* = 7.0 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 131.6, 126.9, 126.5, 123.3, 91.8, 78.4, 53.0, 41.3, 19.9. **HRMS-EI$^+$** m/z calculated for $C_{10}H_{13}NS$ $[M]^+$: 179.0769, found 179.0762.

(±)-*N*,*N*-Dimethyl-4-(trimethylsilyl)but-3-yn-2-amine, **III-5m**.



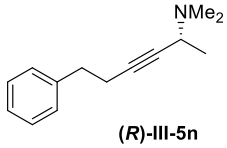
III-5m

From (±)-4-(trimethylsilyl)-3-butyn-2-ol (1.5 g, 10.5 mmol), following the general procedure described above, compound **III-5m** (1.68 g, 9.9 mmol) was obtained in 94% yield as a yellow oil.

^{1}H NMR, ^{13}C NMR and MS data were consistent with literature values.[94] **^{1}H NMR** (300 MHz, $CDCl_3$) δ 3.47 (q, *J* = 7.0 Hz, 1H), 2.25 (s, 6H), 1.31 (d, *J* = 7.1 Hz, 3H), 0.18 (s, 9H).

[94] Aguilar, D.; Contel, M.; Urriolabeitia, E. P. *Chem. Eur. J.* **2010**, *16*, 9287-9296.

(+)-(*R*)-*N*,*N*-Dimethyl-6-phenylhex-3-yn-2-amine, **(*R*)-III-5n**.

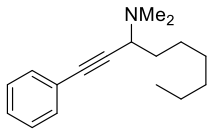


(*R*)-III-5n

From (*S*)-6-phenylhex-3-yn-2-ol (800 mg, 4.6 mmol), following the general procedure described above, compound **(*R*)-III-5n** (845 g, 4.2 mmol) was obtained in 91% yield as an orange oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39 – 7.14 (m, 5H), 3.45 (qt, *J* = 7.0, 2.0 Hz, 1H), 2.86 (t, *J* = 7.5 Hz, 2H), 2.54 (td, *J* = 7.5, 2.0 Hz, 2H), 2.22 (s, 6H), 1.29 (d, *J* = 7.0 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 141.0, 128.7, 128.5, 126.4, 84.5, 78.9, 52.5, 41.3, 35.7, 21.0, 20.4. **HRMS-EI$^+$** m/z calculated for $C_{14}H_{19}N$ $[M]^+$: 201.1517, found 201.1514. **$[\alpha]^{20}_D$**= +18.4 (*c* = 1.0, $CHCl_3$).

(±)-*N*,*N*-Dimethyl-1-phenylnon-1-yn-3-amine, **III-5o**.

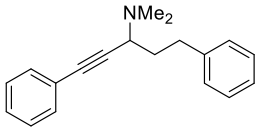


III-5o

From (±)-1-phenylnon-1-yn-3-ol (1.37 g, 6.3 mmol), following the general procedure described above, compound **III-5o** (810 g, 3.3 mmol) was obtained in 53% yield as an orange oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 – 7.41 (m, 2H), 7.34 – 7.24 (m, 3H), 3.52 (t, *J* = 7.3 Hz 1H), 2.33 (s, 6H), 1.73 – 1.64 (m, 2H), 1.57 – 1.41 (m, 2H), 1.36 – 1.27 (m, 6H), 0.89 (t, *J* = 6.7 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 131.9, 128.4, 128.0, 123.6, 87.2, 86.1, 58.4, 41.6, 34.2, 31.9, 29.3, 26.9, 22.8, 14.3. **HRMS-ESI$^+$** m/z calculated for $C_{17}H_{26}N$ $[M+H]^+$: 244.2059, found 244.2056.

(±)-*N*,*N*-Dimethyl-1,5-diphenylpent-1-yn-3-amine, **III-5p**.

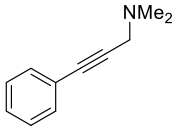


III-5p

From (±)-1,5-diphenylpent-1-yn-3-ol (3.0 g, 12.7 mmol), following the general procedure described above, compound **III-5p** (2.02 g, 7.6 mmol) was obtained in 60% yield as an orange oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61 – 7.47 (m, 2H), 7.45 – 7.23 (m, 8H), 3.59 (t, *J* = 7.6 Hz, 1H), 3.03 – 2.77 (m, 2H), 2.41 (s, 6H), 2.10 (q, *J* = 7.7 Hz, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 141.9, 131.9, 128.7, 128.5, 128.4, 128.0, 126.0, 123.5, 86.8, 86.5, 57.5, 41.6, 35.7, 32.9. **HRMS-EI$^+$** m/z calculated for $C_{19}H_{21}N$ $[M]^+$: 263.1674, found 263.1661.

(±)-*N*,*N*-Dimethyl-3-phenylprop-2-yn-1-amine, **III-5q**.



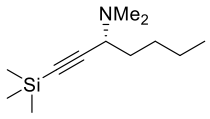
III-5q

From 3-phenylprop-2-yn-1-ol (530 mg, 4 mmol), following the general procedure described above, compound **III-5q** (626 g, 3.9 mmol) was obtained in 98% yield as an orange oil.

^{1}H NMR, ^{13}C NMR and MS data were consistent with literature values.[95] **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.40 – 7.33 (m, 2H), 7.25 – 7.20 (m, 3H), 3.40 (s, 2H), 2.30 (s, 6H).

[95] West, T. H.; Daniels, D. S. B.; Slawin, A. M. Z.; Smith, A. D. *J. Am. Chem. Soc.* **2014**, *136*, 4476-4479.

(–)-(*R*)-*N*,*N*-Dimethyl-1-(trimethylsilyl)hept-1-yn-3-amine, **(*R*)-III-5w**.

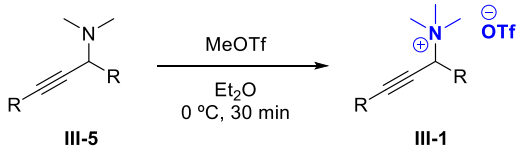


(*R*)-III-5w

From (*S*)-1-(trimethylsilyl)hept-1-yn-3-ol (1.0 g, 5.4 mmol), following the general procedure described above, compound **(*R*)-III-5w** (700 mg, 3.3 mmol) was obtained in 61% yield as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 3.27 (t, *J* = 7.5 Hz, 1H), 2.23 (s, 6H), 1.56 (m, 2H), 1.37 (m, 4H), 0.91 (t, *J* = 7.0 Hz, 3H), 0.17 (s, 9H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 103.8, 89.8, 58.4, 41.4, 33.7, 28.9, 22.6, 14.1, 0.4. **$[\alpha]^{20}_D$**= –5.7 (*c* = 1.0, $CHCl_3$). **HRMS-ESI$^+$** m/z calculated for $C_{12}H_{26}NSi$ $[M+H]^+$: 212.1829, found 212.1829.

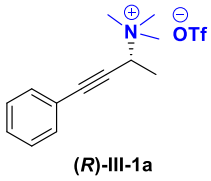
3.6.1.5. Synthesis of propargylic ammonium triflates, 1.



III-5 **III-1**

To a solution of the dimethylamine (1 equiv) in Et_2O (2.0 mL/mmol of amine) was added methyl trifluoromethanesulfonate (1.1 equiv) at 0 ºC. The reaction was stirred for 30 min at 0 ºC and a white solid precipitated. The mixture was filtered through a fritted funnel and was washed with cold Et_2O. The white solid was dried under vacuum for 16 h.

(+)-(*R*)-*N*,*N*,*N*-Trimethyl-4-phenylbut-3-yn-2-aminium trifluoromethanesulfonate, **(*R*)-III-1a**.

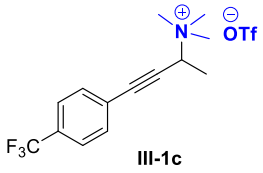


(*R*)-III-1a

From **(*R*)-III-5a** (776 mg, 4.5 mmol), following the general procedure described above, compound **(*R*)-III-1a** (1.47 g, 4.35 mmol) was obtained in 97% yield as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 – 7.43 (m, 2H), 7.44 – 7.31 (m, 3H), 4.81 (q, *J* = 6.8 Hz, 1H), 3.33 (s, 9H), 1.78 (d, *J* = 6.8 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 132.1, 130.1, 128.7, 120.8 (q, $J_{C\text{-}F}$ = 318 Hz), 120.2, 91.4, 80.6, 63.9, 50.9, 16.3. **[α]$^{20}_D$**= +18.6 (*c* = 1.0, $CHCl_3$). **HRMS-FAB$^+$** m/z calculated for $C_{13}H_{18}N$ [M-OTf]$^+$: 188.1439, found 188.1436

(±)-*N*,*N*,*N*-Trimethyl-4-(4-(trifluoromethyl)phenyl)but-3-yn-2-aminium trifluoromethanesulfonate, **III-1c**.

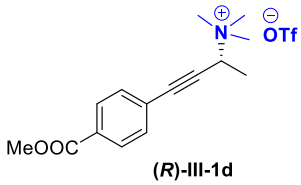


III-1c

From **III-5c** (1.00 g, 4.1 mmol), following the general procedure described above, compound **III-1c** (1.63 g, 4.0 mmol) was obtained in 97% yield as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60 (s, 4H), 4.88 (q, *J* = 6.8 Hz, 1H), 3.31 (s, 9H), 1.77 (d, *J* = 6.8 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 132.5, 131.6 (q, $J_{C\text{-}F}$ = 32.9 Hz), 125.6 (q, $J_{C\text{-}F}$ = 3.7 Hz), 124.0, 123.7 (q, $J_{C\text{-}F}$ = 272.0 Hz), 120.8 (q, $J_{C\text{-}F}$ = 318 Hz), 89.8, 82.7, 63.7, 51.0, 16.1. **HRMS-FAB$^+$** m/z calculated for $C_{14}H_{17}NF_3$ [M-OTf]$^+$: 256.1313, found 256.1315.

(+)-(*R*)-4-(4-(Methoxycarbonyl)phenyl)-*N*,*N*,*N*-trimethylbut-3-yn-2-aminium trifluoromethanesulfonate, **(*R*)-III-1d**.

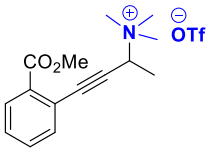


(*R*)-III-1d

From methyl **(*R*)-III-5d** (347 mg, 1.5 mmol), following the general procedure described above, compound **(*R*)-III-1d** (546 mg, 1.4 mmol) was obtained in 92% yield as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 (d, *J* = 8.5 Hz, 2H), 7.53 (d, *J* = 8.5 Hz, 2H), 4.87 (q, *J* = 6.8 Hz, 1H), 3.92 (s, 3H), 3.33 (s, 9H), 1.78 (d, *J* = 6.8 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 166.2, 132.2, 131.4, 129.9, 124.6, 120.8 (q, $J_{C\text{-}F}$ = 318 Hz), 90.7, 83.0, 64.0, 52.5, 51.2, 16.3. **$[\alpha]^{20}_D$**= +24.8 (*c* = 1.0, $CHCl_3$). **HRMS-FAB$^+$** m/z calculated for $C_{15}H_{20}NO_2$ $[M\text{-}OTf]^+$: 246.1494, found 246.1490.

(±)-4-(2-(Methoxycarbonyl)phenyl)-*N*,*N*,*N*-trimethylbut-3-yn-2-aminium trifluoromethanesulfonate, **III-1e**.

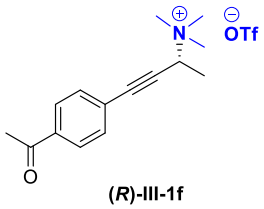


III-1e

From **III-5e** (600 mg, 2.6 mmol), following the general procedure described above, compound **III-1e** (946 mg, 2.4 mmol) was obtained in 94% yield as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95 (d, *J* = 7.7 Hz, 1H), 7.50 (m, 2H), 7.40 (t, *J* = 7.3 Hz, 1H), 4.83 (q, *J* = 6.7 Hz, 1H), 3.84 (s, 3H), 3.33 (s, 9H), 1.73 (d, *J* = 6.7 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 165.6, 134.3, 132.3, 131.4, 130.6, 129.4, 121.3, 120.8 (q, $J_{C\text{-}F}$ = 318 Hz), 89.4, 85.6, 63.8, 52.4, 51.0, 16.0. **HRMS-FAB$^+$** m/z calculated for $C_{15}H_{20}NO_2$ $[M\text{-}OTf]^+$: 246.1488, found 246.1487.

(+)-(*R*)-4-(4-Acetylphenyl)-*N*,*N*,*N*-trimethylbut-3-yn-2-aminium trifluoromethanesulfonate, **(*R*)-III-1f**.

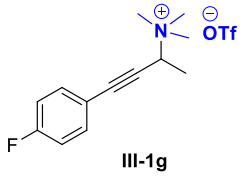


(*R*)-III-1f

From **(*R*)-III-5f** (410 mg, 1.9 mmol), following the general procedure described above, compound **(*R*)-III-1f** (670 mg, 1.8 mmol) was obtained in 93% yield as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94 (d, *J* = 8.4 Hz, 2H), 7.58 (d, *J* = 8.4 Hz, 2H), 4.91 (q, *J* = 6.7 Hz, 1H), 3.34 (s, 9H), 2.61 (s, 3H), 1.80 (d, *J* = 6.7 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 197.3, 137.8, 132.4, 128.5, 124.8, 120.8 (q, $J_{C\text{-}F}$ = 318 Hz), 90.6, 83.4, 63.9, 51.1, 26.8, 16.3. **$[\alpha]^{20}_D$**= +24.8 (*c* = 1.0, $CHCl_3$). **HRMS-FAB$^+$** m/z calculated for $C_{15}H_{20}NO$ $[M\text{-}OTf]^+$: 230.1545, found 230.1543.

(±)-4-(4-Fluorophenyl)-*N*,*N*,*N*-trimethylbut-3-yn-2-aminium trifluoromethanesulfonate, **III-1g**.

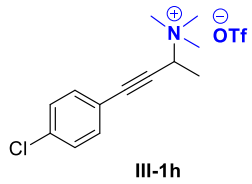


III-1g

From **III-5g** (230 mg, 1.4 mmol), following the general procedure described above, compound **III-1g** (452 mg, 1.3 mmol) was obtained in 91% yield as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47 (dd, *J* = 8.7, 5.3 Hz, 2H), 7.06 (t, *J* = 8.6 Hz, 2H), 4.79 (q, *J* = 6.8 Hz, 1H), 3.31 (s, 9H), 1.76 (d, *J* = 6.8 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 163.4 (d, $J_{C\text{-}F}$ = 252 Hz), 134.2 (d, $J_{C\text{-}F}$ = 8.7 Hz), 134.19, 120.8 (q, $J_{C\text{-}F}$ = 318 Hz), 116.3 (d, $J_{C\text{-}F}$ = 3.5 Hz), 116.0 (d, $J_{C\text{-}F}$ = 22.3 Hz), 90.3, 80.3, 80.3, 63.8, 50.8, 16.1. **HRMS-FAB$^+$** m/z calculated for $C_{13}H_{17}FN$ $[M\text{-}OTf]^+$: 206.1340, found 206.1348.

(±)-4-(4-Chlorophenyl)-*N*,*N*,*N*-trimethylbut-3-yn-2-aminium trifluoromethanesulfonate, **III-1h**.

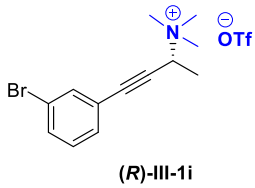


III-1h

From **III-5h** (1.01 g, 4.7 mmol), following the general procedure described above, compound **III-1h** (1.73 g, 4.6 mmol) was obtained in 97% yield as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 (d, *J* = 8.6 Hz, 2H), 7.33 (d, *J* = 8.6 Hz, 2H), 4.82 (q, *J* = 6.8 Hz, 1H), 3.30 (s, 9H), 1.76 (d, *J* = 6.8 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 136.3, 133.4, 129.1, 120.8 (q, $J_{C\text{-}F}$ = 318 Hz), 118.7, 90.4, 81.5, 63.9, 51.0, 16.2. **HRMS-FAB$^+$** m/z calculated for $C_{13}H_{17}NCl$ [M-OTf]$^+$: 222.1044, found 222.1034.

(+)-(*R*)-4-(3-Bromophenyl)-*N*,*N*,*N*-trimethylbut-3-yn-2-aminium trifluoromethanesulfonate, **(*R*)-III-1i**.

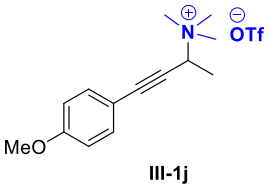


(*R*)-III-1i

From **(*R*)-III-5i** (1.16 mg, 4.6 mmol), following the general procedure described above, compound **(*R*)-III-1i** (1.86 g, 4.5 mmol) was obtained in 97% yield as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 (s, 1H), 7.49 (d, *J* = 8.0 Hz, 1H), 7.38 (d, *J* = 7.6 Hz, 1H), 7.19 (t, *J* = 7.9 Hz, 1H), 4.82 (q, *J* = 6.7 Hz, 1H), 3.26 (s, 9H), 1.72 (d, *J* = 6.7 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 134.6, 133.2, 130.7, 130.2, 120.8 (q, $J_{C\text{-}F}$ = 318 Hz), 122.3, 122.1, 89.7, 81.8, 63.7, 50.9, 16.1. **[α]$^{20}_D$**= +19.6 (*c* = 1.0, $CHCl_3$). **HRMS-FAB$^+$** m/z calculated for $C_{13}H_{17}NBr$ [M-OTf]$^+$: 266.0544, found 266.0548.

(±)-4-(4-Methoxyphenyl)-*N*,*N*,*N*-trimethylbut-3-yn-2-aminium trifluoromethanesulfonate, **III-1j.**

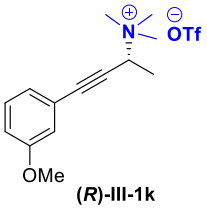


III-1j

From **III-5j** (387 mg, 2.2 mmol), following the general procedure described above, compound **III-1j** (759 mg, 2.1 mmol) was obtained in 94% yield as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39 (d, *J* = 8.9 Hz, 2H), 6.86 (d, *J* = 8.9 Hz, 2H), 4.75 (q, *J* = 6.8 Hz, 1H), 3.82 (s, 3H), 3.29 (s, 9H), 1.74 (d, *J* = 6.8 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 161.0, 133.9, 120.8 (q, $J_{C\text{-}F}$ = 318 Hz), 114.4, 112.2, 91.8, 79.4, 64.3, 55.5, 50.9, 16.5. **HRMS-FAB$^+$** m/z calculated for $C_{15}H_{20}NO$ [M-OTf]$^+$: 218.1545, found 218.1547.

(+)-(*R*)-4-(3-Methoxyphenyl)-*N*,*N*,*N*-trimethylbut-3-yn-2-aminium trifluoromethanesulfonate, **(*R*)-III-1k**.

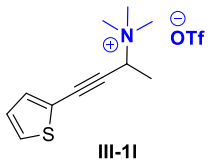


(*R*)-III-1k

From **(*R*)-III-5k** (1.3 g, 6.5 mmol), following the general procedure described above, compound **(*R*)-III-1k** (2.2 g, 6.0 mmol) was obtained in 93% yield as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 (dd, *J* = 8.3, 7.2 Hz, 1H), 7.33 (d, *J* = 7.6 Hz, 1H), 7.28 – 7.21 (m, 2H), 5.08 (q, *J* = 6.7 Hz, 1H), 4.10 (s, 3H), 3.60 (s, 9H), 2.05 (d, *J* = 6.7 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 159.6, 129.9, 124.6, 121.2, 120.8 (q, $J_{C\text{-}F}$ = 318 Hz), 116.9, 116.8, 91.5, 80.3, 64.0, 55.5, 51.0, 16.4. **[α]$^{20}_D$**= +17.1 (*c* = 1.0, $CHCl_3$). **HRMS-ESI$^+$** m/z calculated for $C_{14}H_{20}NO$ [M-OTf]$^+$: 218.1539, found 218.1533.

(±)-*N*,*N*,*N*-Trimethyl-4-(thiophen-2-yl)but-3-yn-2-aminium trifluoromethanesulfonate, **III-1l**.

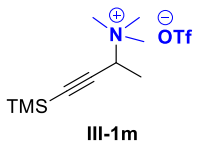


III-1l

From **III-5l** (516 mg, 2.9 mmol), following the general procedure described above, compound **III-1l** (950 mg, 2.8 mmol) was obtained in 96% yield as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (dd, *J* = 5.1, 0.9 Hz, 1H), 7.33 – 7.29 (m, 1H), 6.99 (dd, *J* = 5.1, 3.7 Hz, 1H), 4.82 (q, *J* = 6.8 Hz, 1H), 3.24 (s, 9H), 1.72 (d, *J* = 6.8 Hz, 3H).**^{13}C NMR** (75 MHz, $CDCl_3$) δ 134.7, 129.6, 127.5, 120.8 (q, J_{C-F} = 320.1 Hz), 119.7, 85.0, 84.4, 64.1, 50.9, 16.1. **HRMS-FAB$^+$** m/z calculated for $C_{11}H_{16}NS$ $[M\text{-}OTf]^+$: 194.1003, found 194.0996.

(±)-*N*,*N*,*N*-Trimethyl-4-(trimethylsilyl)but-3-yn-2-aminium trifluoromethanesulfonate, **III-1m**.

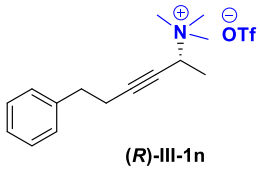


III-1m

From **III-5m** (1.24 g, 7.3 mmol), following the general procedure described above, compound **III-1m** (1.86 g, 5.6 mmol) was obtained in 77% yield as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.53 (q, *J* = 6.7 Hz, 1H), 3.22 (s, 9H), 1.64 (d, *J* = 6.7 Hz, 3H), 0.19 (s, 9H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 120.8 (q, J_{C-F} = 320.0 Hz), 98.3, 96.5, 63.8, 50.8, 16.2, –0.5. **HRMS-FAB$^+$** m/z calculated for $C_{10}H_{22}NSi$ $[M\text{-}OTf]^+$: 184.1522, found 184.1522.

(+)-(*R*)-*N*,*N*,*N*-Trimethyl-6-phenylhex-3-yn-2-aminium trifluoromethanesulfonate, **(*R*)-III-1n**.

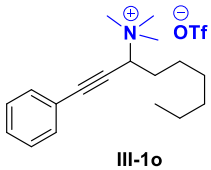


(*R*)-III-1n

From **(*R*)-III-5n** (800 mg, 4.0 mmol), following the general procedure described above, compound **(*R*)-III-1n** (1.35 mg, 3.75 mmol) was obtained in 93% yield as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 – 7.28 (m, 2H), 7.28 – 7.18 (m, 3H), 4.42 (qt, *J* = 6.6, 1.9 Hz, 1H), 3.04 (s, 9H), 2.87 (t, *J* = 7.1 Hz, 2H), 2.71 – 2.54 (td, *J* = 7.1, 1.9 Hz, 2H), 1.57 (d, *J* = 6.6 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 139.7, 128.6, 128.4, 126.8, 120.7 (q, $J_{C\text{-}F}$ = 320.0 Hz), 92.2, 73.5, 63.6, 50.5, 33.8, 20.4, 16.3. **HRMS-FAB$^+$** m/z calculated for $C_{15}H_{22}N$ [M-OTf]$^+$: 216.1752, found 216.1754. **[α]$^{20}_D$**= +7.5 (*c* = 1.0, $CHCl_3$).

(±)-*N*,*N*,*N*-Trimethyl-1-phenylnon-1-yn-3-aminium trifluoromethanesulfonate, **III-1o**.



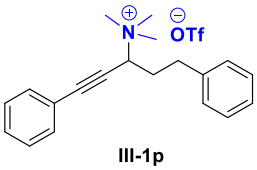
III-1o

From **III-5o** (540 mg, 2.2 mmol), following the general procedure described above, compound **III-1o** (701 mg, 1.7 mmol) was obtained in 78% yield. In this case, a precipitate did not form upon addition of MeOTf. Instead, two distinct layers appeared. The top layer was decanted off. The bottom layer was washed with Et_2O (2 x 10 mL) and then dried under vacuum to give salt **III-1o** as a light yellow tacky oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 (dd, *J* = 7.9, 1.6 Hz, 2H), 7.44 – 7.30 (m, 3H), 4.56 (dd, *J* = 11.5, 3.7 Hz, 1H), 3.31 (s, 9H), 2.08 (m, 1H), 1.85 – 1.69 (m, 1H), 1.69 – 1.23 (m, 8H), 0.87 (t, *J* = 6.6 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 132.2, 130.2, 128.8, 120.8 (q, $J_{C\text{-}F}$ = 318 Hz), 120.3, 92.6,

79.8, 68.9, 51.4, 31.6, 29.1, 28.7, 26.5, 22.5, 14.1. **HRMS-ESI**$^{+}$ m/z calculated for $C_{18}H_{28}N$ [M-OTf]$^{+}$: 258.2216, found 258.2204.

(±)-*N*,*N*,*N*-Trimethyl-1,5-diphenylpent-1-yn-3-aminium trifluoromethanesulfonate, **III-1p**.

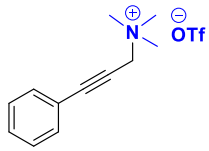


III-1p

From **III-5p** (318 mg, 2.0 mmol), following the general procedure described above, compound **III-1p** (626 mg, 1.9 mmol) was obtained in 95% yield as white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 – 7.45 (m, 2H), 7.45 – 7.33 (m, 3H), 7.32 – 7.22 (m, 4H), 7.18 (m, 1H), 4.57 (dd, *J* = 11.6, 3.5 Hz, 1H), 3.24 (s, 9H), 2.99 (m, 1H), 2.85 (m, 1H), 2.42 (m, 1H), 2.08 (m, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 139.3, 132.3, 130.2, 128.8, 128.8, 128.5, 126.8, 120.8 (q, $J_{C\text{-}F}$ = 320.1 Hz), 120.1, 93.2, 79.3, 68.2, 51.3, 32.3, 30.8. **HRMS-FAB**$^{+}$ m/z calculated for $C_{20}H_{24}N$ [M-OTf]$^{+}$: 278.1903, found 278.1903.

N,*N*,*N*-Trimethyl-3-phenylprop-2-yn-1-aminium trifluoromethanesulfonate, **III-1q**.

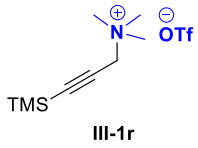


III-1q

From **III-5q** (318 mg, 2.0 mmol), following the general procedure described above, compound **III-1q** (626 mg, 1.9 mmol) was obtained in 97% yield as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 (d, *J* = 6.7 Hz, 2H), 7.42 – 7.29 (m, 3H), 4.51 (s, 2H), 3.33 (s, 9H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 132.3, 130.2, 128.8, 120.8 (q, $J_{C\text{-}F}$ = 319.8 Hz), 120.3, 92.4, 75.9, 57.5, 52.9. **HRMS-FAB**$^{+}$ m/z calculated for $C_{12}H_{16}N$ [M-OTf]$^{+}$: 174.1283, found 174.1277.

N,*N*,*N*-Trimethyl-3-(trimethylsilyl)prop-2-yn-1-aminium trifluoromethanesulfonate, **III-1r**.

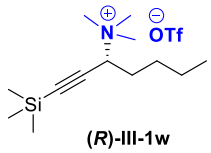


III-1r

From *N*,*N*-dimethyl-3-(trimethylsilyl)prop-2-yn-1-amine (1.6 g, 10.3 mmol), following the general procedure described above, compound **III-1r** (3.23 g, 10.1 mmol) was obtained in 98% yield as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.25 (s, 2H), 3.27 (s, 9H), 0.21 (s, 9H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 120.7 (q, $J_{C\text{-}F}$ = 319.7 Hz), 99.7, 91.7, 57.4, 52.8, –0.5. **HRMS-ESI$^+$** m/z calculated for $C_9H_{20}NSi$ [M-OTf]$^+$: 170.1359, found 170.1358.

(–)-(*R*)-*N*,*N*,*N*-trimethyl-1-(trimethylsilyl)hept-1-yn-3-aminium trifluoromethanesulfonate, **(*R*)-III-1w**.

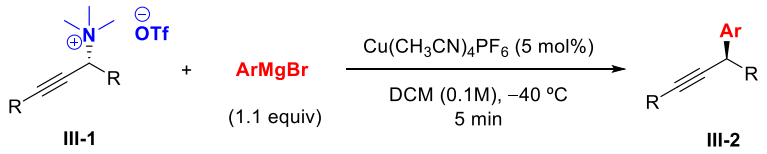


(*R*)-III-1w

From **(*R*)-III-5w** (400 mg, 1.9 mmol), following the general procedure described above, compound **(*R*)-III-1w** (628 mg, 1.7 mmol) was obtained in 88% yield as a white solid.

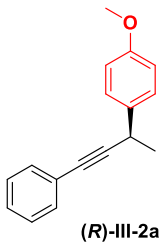
^{1}H NMR (300 MHz, $CDCl_3$) δ 4.28 (dd, *J* = 11.6, 3.8 Hz, 1H), 3.26 (s, 9H), 2.03 (m, 1H), 1.67 (m, 1H), 1.58 – 1.32 (m, 4H), 0.94 (t, *J* = 7.1 Hz, 3H), 0.22 (s, 9H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 120.8 (q, $J_{C\text{-}F}$ = 320.1 Hz), 99.6, 95.8, 68.6, 51.2, 28.5, 22.0, 13.9, –0.48. **$[\alpha]^{20}_D$**= –18.1 (*c* = 1.0, $CHCl_3$). **HRMS-ESI$^+$** m/z calculated for $C_{13}H_{28}NSi$ [M-OTf]$^+$: 226.1985, found 226.1993.

3.6.2. Copper-catalyzed reaction of propargylic ammonium triflates with aryl Grignard reagents.



An oven-dried vial was charged with $[Cu(CH_3CN)_4]PF_6$ (3.8 mg, 0.01 mmol) and the corresponding ammonium salt (0.2 mmol) and sealed with a septum. The vial was connected to an argon-vacuum line, evacuated and backfilled with argon (x3). CH_2Cl_2 (2 mL) was added and the mixture was stirred for 5 min at room temperature. The reaction mixture was cooled to –40 ºC and an aryl magnesium bromide solution in THF (0.22 mmol) was added dropwise. The mixture was stirred at –40 ºC for 5 minutes. Water (0.1 mL) was added and the solution was filtered through a short pad of $MgSO_4$ and rinsed with CH_2Cl_2. The solvent was removed under reduced pressure and the crude product was purified by flash column chromatography using *n*-hexane as eluent.

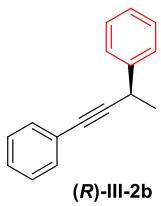
(–)-(*R*)-1-Methoxy-4-(4-phenylbut-3-yn-2-yl)benzene, ***(R)*-III-2a**.



From **(*R*)-III-1a** (67 mg, 0.2 mmol) and 4-methoxyphenylmagnesium bromide (0.22 M in THF, 0.22 mmol) following the general procedure described above, compound **(*R*)-III-2a** (43 mg, 0.18 mmol) was obtained in 90% yield as a yellow oil after flash column chromatography (hex/EtOAc, 95/5). From **(±)-III-1a,** following the same procedure, compound **(±)-III-2a** (42 mg, 0.18 mmol) was obtained in 88% yield.

Compound **(*R*)-III-2a** was obtained in 99:1 enantiomeric ratio determined by SFC using Chiralpak-ID column [CO_2/MeOH (98:2)], 1.0 mL/min, τ_{major}= 10.9 min, τ_{minor}= 12.4 min. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.47 – 7.42 (m, 2H), 7.38 (d, *J* = 8.6 Hz, 2H), 7.33 – 7.27 (m, 3H), 6.90 (d, *J* = 8.6 Hz, 2H), 3.95 (q, *J* = 7.1 Hz, 1H), 3.81 (s, 3H), 1.57 (d, *J* = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 158.5, 135.6, 131.7, 128.3, 128.0, 127.8, 123.9, 114.1, 93.1, 82.4, 55.4, 31.8, 24.7. **$[\alpha]^{20}_D$**= –17.6 (*c* = 1.0, $CHCl_3$). **HRMS-EI$^+$** m/z calculated for $C_{17}H_{16}O$ $[M]^+$: 236.1195, found 236.1183.

(–)-(*R*)-But-1-yne-1,3-diyldibenzene, ***(R)*-III-2b**.

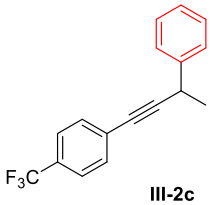


From ***(R)*-III-1a** (67 mg, 0.2 mmol) and phenylmagnesium bromide (0.76M in THF, 0.22 mmol) following the general procedure described above, compound ***(R)*-III-2b** (39 mg, 0.19 mmol) was obtained in 95% yield as a yellow oil. From **(±)-III-1a,** following the same procedure, compound **(±)-III-2b** (37 mg, 0.18 mmol) was obtained in 91% yield.

Compound ***(R)*-III-2b** was obtained in 99:1 enantiomeric ratio determined by SFC using Chiralpak-ID column [CO_2], 1.0 mL/min, τ_{major}= 22.9 min, τ_{minor}= 24.5 min. ^{1}H NMR, ^{13}C NMR and MS data were consistent with literature values. [96] **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.45 (m, 4H), 7.32 (m, 6H), 3.99 (q, *J* = 7.1 Hz, 1H), 1.59 (d, *J* = 7.0 Hz, 3H). **$[\alpha]^{20}_D$**= –16.3 (*c* = 1.0, $CHCl_3$).

[96] García Ruano, J. L.; Marzo, L.; Marcos, V.; Alvarado, C.; Alemán, J. *Chem. Eur. J.* **2012**, *18*, 9775-9779.

(±)-1-(3-Phenylbut-1-yn-1-yl)-4-(trifluoromethyl)benzene, **III-2c**.

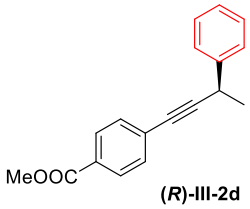


III-2c

From **III-1c** (81 mg, 0.2 mmol) and phenylmagnesium bromide (0.76M in THF, 0.22 mmol) following the general procedure described above, compound **III-2c** (46 mg, 0.17 mmol) was obtained in 84% yield as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 (s, 4H), 7.44 (m, 2H), 7.41 – 7.32 (m, 2H), 7.30 – 7.26 (m, 1H), 4.00 (q, J = 7.1 Hz, 1H), 1.60 (d, J = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 143.0, 132.0, 129.7 (q, $J_{C\text{-}F}$ = 32.6 Hz), 128.8, 127.8 (q, $J_{C\text{-}F}$ = 0.7 Hz), 127.1, 127.0, 125.3 (q, $J_{C\text{-}F}$ = 3.8 Hz), 124.2 (q, $J_{C\text{-}F}$ = 272.0 Hz), 95.5, 81.4, 32.6, 24.4. **HRMS-EI^{+}** m/z calculated for $C_{17}H_{13}F_3$ $[M]^{+}$: 274.0969, found 274.0979.

(–)-Methyl (*R*)-4-(3-phenylbut-1-yn-1-yl)benzoate, ***(R)*-III-2d**.



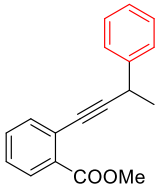
(*R*)-III-2d

From **(*R*)-III-1d** (79 mg, 0.2 mmol) and phenylmagnesium bromide (0.76 M in THF, 0.22 mmol) following the general procedure described above, compound **(*R*)-III-2d** (43 mg, 0.16 mmol) was obtained in 81% yield as a yellow oil after flash column chromatography (hex/EtOAc, 95/5). From **(±)-III-1d**, following the same procedure, compound **(±)-III-2d** (44 mg, 0.17 mmol) was obtained in 83% yield.

Compound **(*R*)-III-2d** was obtained in 99:1 enantiomeric ratio determined by SFC using Chiralpak-ID column [CO_2/MeOH (95:5)], 1.0 mL/min, τ_{major}= 13.3 min, τ_{minor}= 14.4 min. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.99 (d, J = 8.6 Hz, 2H), 7.51 (d, J = 8.6 Hz, 2H), 7.46 (d, J = 7.3 Hz, 2H), 7.37 (t, J = 7.3 Hz, 2H), 7.27 (m, 1H), 4.08 – 3.95 (m, 1H), 3.92 (s, 3H), 1.61 (d, J =

7.2 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 166.7, 142.9, 131.6, 129.4, 129.1, 128.7, 128.6, 126.9, 126.9, 96.0, 81.9, 52.2, 32.6, 24.3. **$[\alpha]^{20}_D$**= –12.5 (*c* = 1.0, $CHCl_3$). **HRMS-EI$^+$** m/z calculated for $C_{18}H_{16}O_2$ $[M]^+$: 264.1150, found 264.1140.

(±)-Methyl 2-(3-phenylbut-1-yn-1-yl)benzoate, **III-2e**.

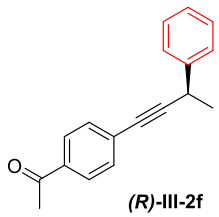


III-2e

From **III-1e** (79 mg, 0.2 mmol) and phenylmagnesium bromide (0.76 M in THF, 0.22 mmol) following the general procedure described above, compound **III-2e** (31 mg, 0.12 mmol) was obtained in 60% yield as a yellow oil after flash column chromatography (hex/ EtOAc, 95/5).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.56 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.51 (d, *J* = 7.4 Hz, 2H), 7.44 (td, *J* = 7.6, 1.5 Hz, 1H), 7.35 (d, *J* = 7.7 Hz, 2H), 7.30 – 7.23 (m, 1H), 4.06 (q, *J* = 7.1 Hz, 1H), 3.87 (s, 3H), 1.63 (d, *J* = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 167.2, 143.3, 134.2, 132.3, 131.6, 130.3, 128.7, 127.6, 127.1, 126.8, 124.1, 97.9, 81.3, 52.1, 32.9, 24.5. **HRMS-EI$^+$** m/z calculated for $C_{18}H_{15}O_2$ $[M-1]^+$: 263.1072, found 263.1061.

(–)-(*R*)-1-[4-(3-Phenylbut-1-yn-1-yl)phenyl]ethan-1-one, **(*R*)-III-2f**.



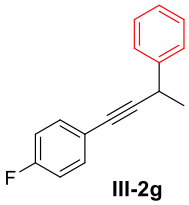
***(R)*-III-2f**

From **(*R*)-III-1f** (73 mg, 0.2 mmol) and phenylmagnesium bromide (0.76 M in THF, 0.22 mmol) following the general procedure described above, compound **(*R*)-III-2f** (26 mg, 0.10 mmol) was obtained in 52% yield as a yellow oil after flash column chromatography (hex/ EtOAc, 95:5). From **(±)-III-1f,** following

the same procedure, compound **(±)-III-2f** (26 mg, 0.10 mmol) was obtained in 52% yield.

Compound **(*R*)-III-2f** was obtained in 98:2 enantiomeric ratio determined by SFC using Chiralpak-ID column [CO_2/MeOH (98:2)], 1.0 mL/min, τ_{major}= 26.3 min, τ_{minor}= 24.6 min. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.86 (d, *J* = 8.4 Hz, 2H), 7.48 (d, *J* = 8.4 Hz, 2H), 7.41 (d, *J* = 7.3 Hz, 2H), 7.33 (t, *J* = 7.4 Hz, 2H), 7.24 (d, *J* = 7.6 Hz, 1H), 3.98 (q, *J* = 7.1 Hz, 1H), 2.56 (s, 3H), 1.57 (d, *J* = 7.2 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 197.5, 143.0, 136.1, 131.9, 128.9, 128.8, 128.3, 127.0, 127.0, 96.5, 82.0, 32.7, 26.7, 24.4. **$[\alpha]^{20}_D$**= –35.7 (*c* = 1.0, $CHCl_3$). **HRMS-EI$^+$** m/z calculated for $C_{18}H_{16}O$ $[M]^+$: 248.1201, found 248.1201.

(±)-1-Fluoro-4-(3-phenylbut-1-yn-1-yl)benzene, **III-2g**.

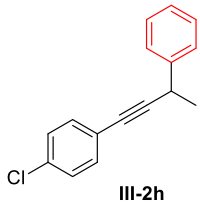


III-2g

From **III-1g** (71 mg, 0.2 mmol) and phenylmagnesium bromide (0.76 M in THF, 0.22 mmol) following the general procedure described above, compound **III-2g** (40 mg, 0.18 mmol) was obtained in 90% yield as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39 (m, 6H), 7.27 (m, 1H), 6.99 (t, *J* = 8.7 Hz, 2H), 3.97 (q, *J* = 7.1 Hz, 1H), 1.58 (d, *J* = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 162.2 (d, $J_{C\text{-}F}$ = 248.4 Hz), 143.2, 133.5 (d, $J_{C\text{-}F}$ = 8.3 Hz), 128.6, 126.9, 126.7, 119.8 (d, $J_{C\text{-}F}$ = 3.5 Hz), 115.4 (d, $J_{C\text{-}F}$ = 22.0 Hz), 92.3, 81.4, 32.4, 24.5. **HRMS-EI$^+$** m/z calculated for $C_{16}H_{13}F$ $[M]^+$: 224.1001, found 224.0996.

(±)-1-Chloro-4-(3-phenylbut-1-yn-1-yl)benzene, **III-2h**.

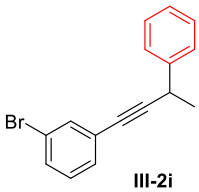


III-2h

From **III-1h** (74 mg, 0.2 mmol) and phenylmagnesium bromide (0.76 M in THF, 0.22 mmol) following the general procedure described above, compound **III-2h** (46 mg, 0.19 mmol) was obtained in 96% yield as a yellow oil. The reaction was also carried out in gram scale, from **III-1h** (1.0 g, 2.7 mmol) and phenylmagnesium bromide (0.76 M in THF, 3.0 mmol) affording compound **III-2h** (604 mg, 2.51 mmol) in 93% yield as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 (d, *J* = 7.5 Hz, 2H), 7.33 (m, 4H), 7.25 (m, 3H), 3.95 (q, *J* = 7.1 Hz, 1H), 1.56 (d, *J* = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 143.2, 133.8, 133.0, 128.7, 128.6, 127.0, 126.9, 122.4, 93.8, 81.5, 32.6, 24.5. **HRMS-EI$^+$** m/z calculated for $C_{16}H_{13}Cl$ $[M]^+$: 240.0700, found 240.0692.

(±)-1-Bromo-3-(3-phenylbut-1-yn-1-yl)benzene, **III-2i**.

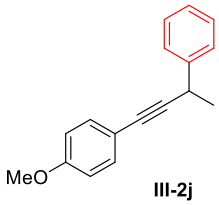


III-2i

From **III-1i** (83 mg, 0.2 mmol) and phenylmagnesium bromide (0.76 M in THF, 0.22 mmol) following the general procedure described above, compound **III-2i** (53 mg, 0.19 mmol) was obtained in 93% yield as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60 (t, *J* = 1.7 Hz, 1H), 7.46 – 7.39 (m, 3H), 7.39 – 7.32 (m, 3H), 7.29 – 7.26 (m, 1H), 7.16 (t, *J* = 7.9 Hz, 1H), 3.98 (q, *J* = 7.1 Hz, 1H), 1.58 (d, *J* = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 143.0, 134.5, 131.0, 130.3, 129.8, 128.7, 127.0, 126.9, 125.9, 122.2, 94.3, 81.1, 32.6, 24.4. **HRMS-EI$^+$** m/z calculated for $C_{16}H_{13}Br$ $[M]^+$: 284.0201, found 284.0188.

(±)-1-Methoxy-4-(3-phenylbut-1-yn-1-yl)benzene, **III-2j**.

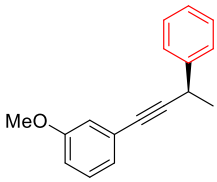


III-2j

From **III-1j** (74 mg, 0.2 mmol) and phenylmagnesium bromide (0.76 M in THF, 0.22 mmol) following the general procedure described above, compound **III-2j** (45 mg, 0.19 mmol) was obtained in 94% yield as a yellow oil after flash column chromatography (hex/ EtOAc, 95/5).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 (d, *J* = 7.3 Hz, 2H), 7.36 (m, 4H), 7.30 – 7.20 (m, 1H), 6.83 (d, *J* = 8.8 Hz, 2H), 3.98 (q, *J* = 7.1 Hz, 1H), 3.81 (s, 3H), 1.58 (d, *J* = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 159.3, 143.7, 133.1, 128.7, 127.1, 126.7, 116.0, 113.9, 91.2, 82.3, 55.4, 32.6, 24.7. **HRMS-EI$^+$** m/z calculated for $C_{17}H_{16}O$ $[M]^+$: 236.1201, found 236.1195.

(–)-(*R*)-1-Methoxy-3-(3-phenylbut-1-yn-1-yl)benzene, ***(R)*-III-2k**.



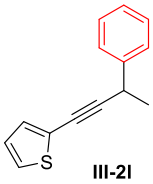
***(R)*-III-2k**

From **(*R*)-III-1k** (73 mg, 0.2 mmol) and phenylmagnesium bromide (0.76 M in THF, 0.22 mmol) following the general procedure described above, compound **(*R*)-III-2k** (46 mg, 0.19 mmol) was obtained in 97% yield as a yellow oil after flash column chromatography (hex/ EtOAc, 95/5). From **(±)-III-1k,** following the same procedure, compound **(±)-III-2k** (44 mg, 0.19 mmol) was obtained in 93% yield.

Compound **(*R*)-III-2k** was obtained with a 98:2 enantiomeric ratio determined by SFC using Chiralpak-IB column [CO_2/MeOH (99.5:0.5)], 1.0 mL/min, τ_{major}= 20.9 min, τ_{minor}= 20.2 min. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.53 – 7.44 (m, 2H), 7.42 – 7.33 (m, 2H), 7.32 – 7.26 (m, 1H), 7.23 (m, 1H), 7.07 (dt, *J* = 7.6, 1.1 Hz, 1H), 7.00 (m, 1H), 6.87 (ddd, *J* = 8.3, 2.6, 0.9

Hz, 1H), 4.01 (q, *J* = 7.1 Hz, 1H), 3.81 (s, 3H), 1.61 (d, *J* = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 159.5, 143.4, 129.4, 128.7, 127.1, 126.8, 124.9, 124.4, 116.6, 114.5, 92.6, 82.5, 55.4, 32.6, 24.6. **$[\alpha]^{20}_D$**= −18.8 (*c* = 1.0, $CHCl_3$). **HRMS-EI$^+$** m/z calculated for $C_{17}H_{16}O$ $[M]^+$: 236.1195, found 236.1188.

(±)-2-(3-Phenylbut-1-yn-1-yl)thiophene, **III-2l**.

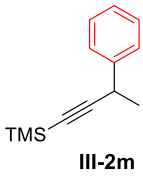


III-2l

From **III-1l** (69 mg, 0.2 mmol) and phenylmagnesium bromide (0.76 M in THF, 0.22 mmol) following the general procedure described above, compound **III-2l** (34 mg, 0.16 mmol) was obtained in 81% yield as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45 (d, *J* = 7.3 Hz, 2H), 7.36 (t, *J* = 7.4 Hz, 2H), 7.28 (d, *J* = 7.1 Hz, 1H), 7.23 – 7.17 (m, 2H), 6.96 (dd, *J* = 5.1, 3.6 Hz, 1H), 4.02 (q, *J* = 7.1 Hz, 1H), 1.60 (d, *J* = 7.2 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 143.1, 131.4, 128.7, 127.1, 126.9, 126.9, 126.4, 124.0, 96.6, 75.7, 32.9, 24.4. **HRMS-EI$^+$** m/z calculated for $C_{14}H_{12}S$ $[M]^+$: 212.0654, found 212.0651.

(±)-Trimethyl(3-phenylbut-1-yn-1-yl)silane, **III-2m**.



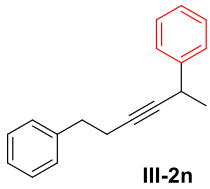
III-2m

From **III-1m** (67 mg, 0.2 mmol) and phenylmagnesium bromide (0.76 M in THF, 0.22 mmol) following the general procedure described above, compound **III-2m** (32 mg, 0.16 mmol) was obtained in 80% yield as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 – 7.29 (m, 4H), 7.26 (m, 1H), 3.80 (q, *J* = 7.1 Hz, 1H), 1.50 (d, *J* = 7.2 Hz, 3H), 0.20 (s, 9H). **^{13}C NMR** (75

MHz, $CDCl_3$) δ 143.20, 128.62, 127.02, 126.72, 109.63, 86.36, 32.95, 24.79, 0.31. **HRMS-EI**$^+$ m/z calculated for $C_{13}H_{18}Si$ $[M]^+$: 202.1172, found 202.1171.

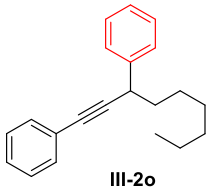
(±)-Hex-3-yne-1,5-diyldibenzene, **III-2n**.



From **III-1n** (73 mg, 0.2 mmol) and phenylmagnesium bromide (0.76 M in THF, 0.22 mmol) following the general procedure described above, compound **III-2n** (41 mg, 0.18 mmol) was obtained in 88% yield as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39 – 7.29 (m, 6H), 7.29 – 7.22 (m, 4H), 3.76 (qt, *J* = 7.1, 2.1 Hz, 1H), 2.88 (t, *J* = 7.5 Hz, 2H), 2.56 (td, *J* = 7.5, 2.1 Hz, 2H), 1.48 (d, *J* = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 143.9, 141.0, 128.6, 128.5, 128.4, 126.9, 126.5, 126.2, 83.8, 81.6, 35.5, 32.0, 24.8, 21.1. **HRMS-EI**$^+$ m/z calculated for $C_{18}H_{18}$ $[M]^+$: 234.1409, found 234.1396.

(±)-Non-1-yne-1,3-diyldibenzene, **III-2o**.

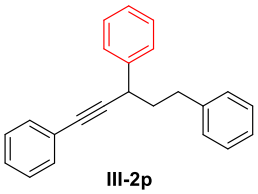


From **III-1o** (81 mg, 0.2 mmol) and phenylmagnesium bromide (0.76 M in THF, 0.22 mmol) following the general procedure described above, compound **III-2o** (41 mg, 0.15 mmol) was obtained in 73% yield as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24 (m, 4H), 7.19 – 7.01 (m, 6H), 3.64 (t, *J* = 7.2 Hz, 1H), 1.64 (m, 2H), 1.31 (m, 2H), 1.18 – 1.04 (m, 6H), 0.69 (t, *J* = 6.6 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 142.4, 131.7, 128.5,

128.2, 127.7, 127.5, 126.6, 123.9, 91.8, 83.2, 38.7, 38.5, 31.8, 29.0, 27.4, 22.6, 14.1. **HRMS-EI$^+$** m/z calculated for $C_{21}H_{24}$ $[M]^+$: 276.1872, found 276.1870.

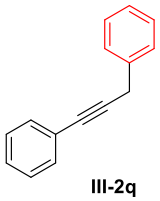
(±)-Pent-1-yne-1,3,5-triyltribenzene, **III-2p**.



From **III-1p** (86 mg, 0.2 mmol) and phenylmagnesium bromide (0.76 M in THF, 0.22 mmol) following the general procedure described above, compound **III-2p** (48 mg, 0.16 mmol) was obtained in 81% yield as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 (m, 2H), 7.49 – 7.43 (m, 2H), 7.42 – 7.19 (m, 11H), 3.98 – 3.83 (m, 1H), 2.99 – 2.78 (m, 2H), 2.26 – 2.07 (m, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 142.0, 141.8, 131.9, 128.7, 128.6, 128.4, 128.0, 127.7, 127.0, 126.1, 123.9, 91.4, 84.0, 40.3, 38.0, 33.8. **HRMS-EI$^+$** m/z calculated for $C_{23}H_{20}$ $[M]^+$: 296.1559, found 296.1552.

Prop-1-yne-1,3-diyldibenzene, **III-2q**.

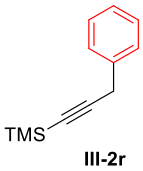


From **III-1q** (65 mg, 0.2 mmol) and phenylmagnesium bromide (0.76 M in THF, 0.22 mmol) following the general procedure described above, compound **III-2q** (20 mg, 0.10 mmol) was obtained in 50% yield as a yellow oil.

^{1}H NMR, ^{13}C NMR and MS data were consistent with literature values.[97]
^{1}H NMR (300 MHz, $CDCl_3$) δ, 7.44 (m, 4H), 7.30 (m, 6H), 3.85 (s, 2H).

[97] Martin, R.; Fustner, A. *Angew. Chem. Int. Ed*. **2004**, *43*, 3955.

Trimethyl(3-phenylprop-1-yn-1-yl)silane, **III-2r**.

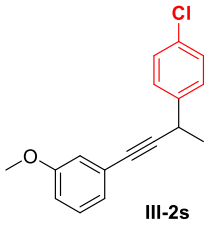


III-2r

From **III-1r** (64 mg, 0.2 mmol) and phenylmagnesium bromide (0.76 M in THF, 0.22 mmol) following the general procedure described above, compound **III-2r** (26 mg, 0.14 mmol) was obtained in 69% yield as a yellow oil.

^{1}H NMR, ^{13}C NMR and MS data were consistent with literature values.[97] **^{1}H NMR** (300 MHz, CDCl3) δ 7.17 – 7.02 (m, 5H), 3.47 (s, 2H), 0.03 – -0.09 (m, 9H).

(±)-1-(3-(4-Chlorophenyl)but-1-yn-1-yl)-3-methoxybenzene, **III-2s**.

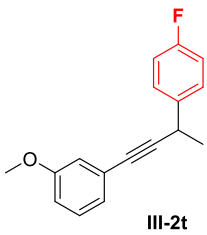


III-2s

From **III-1k** (67 mg, 0.2 mmol) and 4-chlorophenylmagnesium bromide (0.81 M in THF, 0.22 mmol) following the general procedure described above, compound **III-2s** (52 mg, 0.19 mmol) was obtained in 95% yield as a yellow oil after flash column chromatography (hex/ EtOAc, 95/5).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (d, *J* = 8.5 Hz, 2H), 7.23 (d, *J* = 8.5 Hz, 2H), 7.14 (dd, *J* = 15.2, 7.4 Hz, 1H), 6.99 – 6.92 (m, 1H), 6.91 – 6.86 (m, 1H), 6.78 (ddd, *J* = 8.3, 2.6, 0.9 Hz, 1H), 3.88 (q, *J* = 7.1 Hz, 1H), 3.72 (s, 3H), 1.48 (d, *J* = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 159.3, 141.8, 132.4, 129.3, 128.7, 128.3, 124.5, 124.2, 116.5, 114.5, 91.8, 82.7, 55.3, 31.9, 24.4. **HRMS-EI^{+}** m/z calculated for $C_{17}H_{15}OCl$ $[M]^{+}$: 270.0811, found 270.0802.

(±)-1-[3-(4-Fluorophenyl)but-1-yn-1-yl]-3-methoxybenzene, **III-2t**.

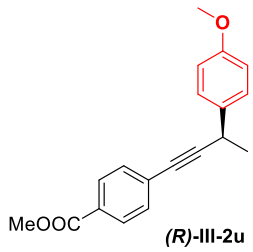


III-2t

From **III-1k** (67 mg, 0.2 mmol) and 4-fluorophenylmagnesium bromide (0.76 M in THF, 0.22 mmol) following the general procedure described above, compound **III-2t** (49 mg, 0.19 mmol) was obtained in 93% yield as a yellow oil after flash column chromatography (*n*-hexane/ EtOAc 95/5).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 – 7.28 (m, 2H), 7.13 (dd, *J* = 14.6, 6.6 Hz, 1H), 6.99 – 6.86 (m, 4H), 6.77 (ddd, *J* = 8.3, 2.6, 0.9 Hz, 1H), 3.88 (q, *J* = 7.1 Hz, 1H), 3.71 (s, 3H), 1.48 (d, *J* = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 161.7 (d, $J_{C\text{-}F}$ = 244.6 Hz), 159.3, 139.0 (d, $J_{C\text{-}F}$ = 3.1 Hz), 129.3, 128.4 (d, $J_{C\text{-}F}$ = 8.0 Hz), 124.6, 124.2, 116.5, 115.3 (d, $J_{C\text{-}F}$ = 21.4 Hz), 114.5, 92.2, 82.6, 55.3, 31.8, 24.5. **HRMS-EI$^+$** m/z calculated for $C_{17}H_{15}OF$ $[M]^+$: 254.1107, found 254.1085.

(–)-(*R*)-Methyl 4-[3-(4-methoxyphenyl)but-1-yn-1-yl]benzoate, ***(R)-III*-2u**.



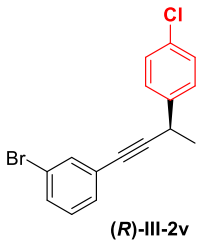
(R)-III-2u

From **(*R*)-III-1d** (79 mg, 0.2 mmol) and 4-methoxyphenylmagnesium bromide (0.76 M in THF, 0.22 mmol) following the general procedure described above, compound **(*R*)-III-2u** (50 mg, 0.17 mmol) was obtained in 84% yield as a yellow oil after flash column chromatography (n-hexane/EtOAc 90/10). From **(±)-III-1d,** following the same procedure, compound **(±)-III-2u** (49 mg, 0.17 mmol) was obtained in 82% yield.

Compound **(*R*)-III-2u** was obtained in 99:1 enantiomeric ratio determined by SFC using Chiralpak-ID column [CO_2/MeOH (95:5)], 1.0 mL/min, τ_{major}= 23.0 min, τ_{minor}= 25.6 min. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.97 (d, *J*

= 8.5 Hz, 2H), 7.49 (d, *J* = 8.5 Hz, 2H), 7.35 (d, *J* = 8.7 Hz, 2H), 6.89 (d, *J* = 8.7 Hz, 2H), 3.96 (q, *J* = 7.1 Hz, 1H), 3.91 (s, 3H), 3.81 (s, 3H), 1.57 (d, *J* = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 166.8, 158.6, 135.1, 131.7, 129.5, 129.2, 128.7, 128.0, 114.2, 96.5, 81.8, 55.5, 52.3, 31.9, 24.5. **$[\alpha]^{20}_D$**= –16.5 (*c* = 1.0, $CHCl_3$). **HRMS-EI$^+$** m/z calculated for $C_{19}H_{18}O_3$ $[M]^+$: 294.1256, found 294.1253.

(–)-(*R*)-1-Bromo-3-[3-(4-chlorophenyl)but-1-yn-1-yl]benzene, **(*R*)-III-2v**.

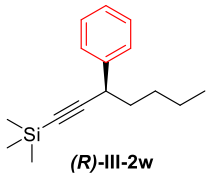


(*R*)-III-2v

From **(*R*)-III-1i** (83 mg, 0.2 mmol) and 4-chlorophenylmagnesium bromide (0.86 M in THF, 0.22 mmol) following the general procedure described above, compound **(*R*)-III-2v** (48 mg, 0.16 mmol) was obtained in 79% yield as a yellow oil. From **(±)-III-1i,** following the same procedure, compound **(±)-III-2v** (52 mg, 0.17 mmol) was obtained in 83% yield.

Compound **(*R*)-III-2v** was obtained in 99:1 enantiomeric ratio determined by SFC using Chiralpak-IA column [CO_2/MeOH (99.5:0.5)], 1.0 mL/min, τ_{major}= 28.0 min, τ_{minor}= 26.4 min. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.59 (s, 1H), 7.43 (d, *J* = 8.0 Hz, 1H), 7.39 – 7.29 (m, 5H), 7.17 (t, *J* = 7.9 Hz, 1H), 3.95 (q, *J* = 7.1 Hz, 1H), 1.56 (d, *J* = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 141.6, 134.5, 132.7, 131.2, 130.3, 129.8, 128.9, 128.4, 125.6, 122.2, 93.6, 81.4, 32.0, 24.4. **$[\alpha]^{20}_D$**= –25.1 (*c* = 1.0, $CHCl_3$). **HRMS-EI$^+$** m/z calculated for $C_{16}H_{12}BrCl$ $[M]^+$: 317.9811, found 317.9799.

(+)-(*R*)-Trimethyl(3-phenylhept-1-yn-1-yl)silane, **(*R*)-III-2w**.

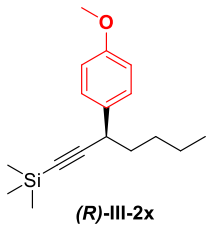


***(R)*-III-2w**

From **(*R*)-III-1w** (75 mg, 0.2 mmol) and 4-methoxyphenylmagnesium bromide (0.76 M in THF, 0.22 mmol) following the general procedure described above, compound **(*R*)-III-2w** (45 mg, 0.18 mmol) was obtained in 92% yield as a yellow oil after flash column chromatography. From **(±)-III-1w,** following the same procedure, compound **(±)-III-2w** (41 mg, 0.17 mmol) was obtained in 84% yield.

Compound **(*R*)-III-2w** was obtained in 93:7 enantiomeric ratio determined by GC on a Chirasil Dex-CB column (100→130 °C @ 10 °C/min, hold 10 min, then →170 °C @ 9 °C/min, hold 5 min; flow rate 1.0 mL/min.). τ_{major}= 17.0 min, τ_{minor}= 16.9 min. ^{1}H NMR, ^{13}C NMR and MS data were consistent with literature values.[51] **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.43 – 7.21 (m, 11H), 3.66 (t, *J* = 7.2 Hz, 2H), 1.85 – 1.68 (m, 4H), 1.56 – 1.24 (m, 8H), 0.91 (t, *J* = 6.9 Hz, 6H), 0.21 (s, 17H). **$[\alpha]^{20}_{D}$**= +13.8 (*c* = 1.0, $CHCl_3$).

(+)-(*R*)-(3-(4-Methoxyphenyl)hept-1-yn-1-yl)trimethylsilane, **(*R*)-III-2x**.



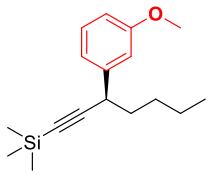
***(R)*-III-2x**

From **(*R*)-III-1w** (75 mg, 0.2 mmol) and 4-methoxyphenylmagnesium bromide (0.76 M in THF, 0.22 mmol) following the general procedure described above, compound **(*R*)-III-2x** (45 mg, 0.16 mmol) was obtained in 82% yield as a yellow oil after flash column chromatography (hex/EtOAc, 98/2). From **(±)-III-1w,** following the same procedure, compound **(±)-III-2x** (49 mg, 0.18 mmol) was obtained in 89% yield.

^{1}H NMR, ^{13}C NMR and MS data were consistent with literature values.[52] **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.6 Hz, 2H), 6.86 (d, *J* = 8.7 Hz, 2H), 3.81 (d, *J* = 4.9 Hz, 3H), 3.59 (t, *J* = 7.2 Hz, 1H), 1.78 – 1.63 (m, 2H), 1.46 – 1.23 (m, 4H), 0.89 (t, *J* = 7.1 Hz, 3H), 0.18 (s, 9H). **[α]$^{20}_{D}$**= +7.9 (*c* = 1.0, $CHCl_3$).

Compound **(*R*)-III-2x** was transformed into **(*S*)-III-7x** through desilylation to determine the enantiomeric ratio (See compound **(*S*)-III-7x**, page SI-33).

(+)-(*R*)-[3-(3-Methoxyphenyl)hept-1-yn-1-yl]trimethylsilane, **(*R*)-III-2y**.



***(R)*-III-2y**

From **(*R*)-III-1w** (75 mg, 0.2 mmol) and 3-methoxyphenylmagnesium bromide (0.78 M in THF, 0.22 mmol) following the general procedure described above, compound **(*R*)-III-2y** (48 mg, 0.17 mmol) was obtained in 87% yield as a yellow oil after flash column chromatography (hex/EtOAc, 98/2). From **(±)-III-1w,** following the same procedure, compound **(±)-III-2y** (45 mg, 0.16 mmol) was obtained in 82% yield.

^{1}H NMR, ^{13}C NMR and MS data were consistent with literature values.[52] **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.23 – 7.18 (m, 1H), 6.92 (m, 2H), 6.77 (m, 1H), 3.81 (s, 3H), 3.61 (t, *J* = 7.2 Hz, 1H), 1.72 (m, 2H), 1.49 – 1.24 (m, 4H), 0.89 (t, *J* = 7.0 Hz, 3H), 0.18 (s, 9H). **[α]$^{20}_{D}$**= +8.2 (*c* = 1.0, $CHCl_3$).

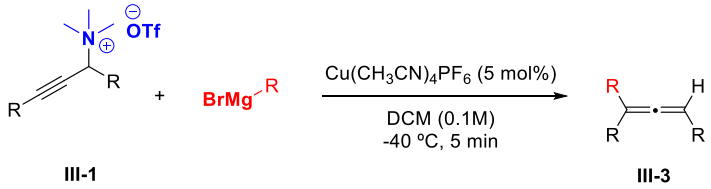
Compound ***(R)*-III-2y** was transformed into **(*S*)-III-7y** through desilylation to determine the enantiomeric ratio (See compound **(*S*)-III-7y**).

3.6.3. Preparation of (4-Phenylbutyl)magnesium bromide solution

An oven-dried flask was charged with magnesium (72 mg, 3 mmol, 1 equiv) and a couple of crystals of iodine under Ar atmosphere. Dry THF (6 mL) was added and the mixture was stirred for 2 min. (4-bromobutyl)benzene was added dropwise to the mixture observing a gentle reflux. The mixture was stirred for 2h and then, it was allowed to rest for 24h. The supernatant was filtered, and the solution was tritrated to determine its concentration (0,43M).

3.6.4. Copper-catalyzed reaction of propargylic ammonium triflates with alkyl Grignard reagents.

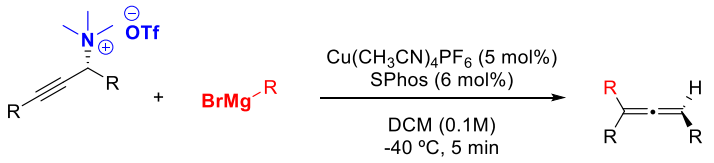
*3.6.4.1. General procedure for the reactions of (±)-propargylic ammonium salts (**III-1**) with alkylmagnesium halides.*



III-1 **III-3**

An oven-dried vial was charged with $[Cu(CH_3CN)_4]PF_6$ (3.8 mg, 0.01 mmol) and the correspondent ammonium salt **III-1** (0.2 mmol) and sealed with a septum. The vial was connected to an argon-vacuum line, evacuated and backfilled with argon (x3). DCM (2 mL) was added and the mixture was stirred for 5 min at room temperature. The reaction mixture was cooled to -40 ºC and the alkyl magnesium bromide solution in THF (0.22 mmol) was added dropwise and the mixture was stirred at -40 ºC for 5 minutes. After total conversion observed by TLC (5 minutes), water (0.1 mL) was added and the solution was filtered through a short pad of $MgSO_4$ and rinsed with DCM. Solvent was removed under reduced pressure and the crude product was purified by flash column chromatography.

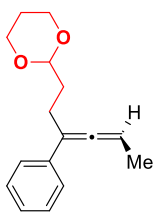
3.6.4.2. General procedure for the reactions of enantiopure propargylic ammonium salts with alkylmagnesium halides.



(*R*)-III-1 **(*R*)-III-3**

An oven-dried vial was charged with $[Cu(CH_3CN)_4]PF_6$ (3.8 mg, 0.01 mmol), Sphos (4.9 mg, 0.012 mmol) and the correspondent ammonium salt (0.2 mmol) and sealed with a septum. The vial was connected to an argon-vacuum line, evacuated and backfilled with argon (x3). DCM (2 mL) was added and the mixture was stirred for 5 min at room temperature. The reaction mixture was cooled to -40 ºC and the alkyl magnesium bromide solution in THF (0.22 mmol) was added dropwise and the mixture was stirred at -40 ºC for 5 minutes. After total conversion observed by TLC (5 minutes), water (0.1 mL) was added and the solution was filtered through a short pad of $MgSO_4$ and rinsed with DCM. Solvent was removed under reduced pressure and the crude product was purified by flash column chromatography.

(–)-(*R*)-2-(3-phenylhexa-3,4-dien-1-yl)-1,3-dioxane, **(*R*)-III-3a**.



(*R*)-III-3a

From **(*R*)-III-1a** (67 mg, 0.2 mmol) and (1,3-Dioxan-2-ylethyl)magnesium bromide solution in THF (0.22 mmol) following the general procedure described above, compound **(*R*)-III-3a** (44 mg, 0.18 mmol) was obtained in 90% yield as a pale yellow oil, after purification by flash column chromatography (cyclohexane/EtOAc 95:5). From **III-1a,** following the same procedure

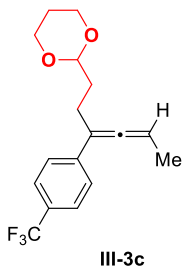
without Sphos, compound **III-3a** (42 mg, 0.17 mmol) was obtained in 86% yield.

^{1}H NMR, ^{13}C NMR and MS data for **III-3a** were consistent with literature values.[98] **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.43 – 7.14 (m, 5H), 5.50 (qt, *J* = 6.9, 3.3 Hz, 1H), 4.63 (t, *J* = 5.2 Hz, 1H), 4.17 – 4.07 (m, 2H), 3.83 – 3.71 (m, 2H), 2.59 – 2.40 (m, 2H), 2.19 – 2.01 (m, 1H), 1.90 – 1.81 (m, 2H), 1.76 (d, *J* = 7.0 Hz, 3H), 1.40 – 1.31 (m, 1H).

Compound **(*R*)-III-3a** was obtained in 98:2 enantiomeric ratio determined by SFC using Chiralpak-ID column [CO_2/MeOH (98:2)], 1.0 mL/min, τ_{major}= 12.9 min, τ_{minor}= 14.4 min. **$[\alpha]^{25}_{D}$**= –64.1 (*c* = 1.0, $CHCl_3$).

The reaction was also carried out in gram scale, from **(*R*)-III-1a** (1.0 g, 2.96 mmol) and (1,3-dioxan-2-ylethyl)magnesium bromide solution in THF (3.3 mmol) affording compound **(*R*)-III-3a** (614 mg, 2.47 mmol) in 85% yield as a yellow oil and enantiomeric ratio of 98:2.

(±)-2-(3-(4-(Trifluoromethyl)phenyl)hexa-3,4-dien-1-yl)-1,3-dioxane, **III-3c**.



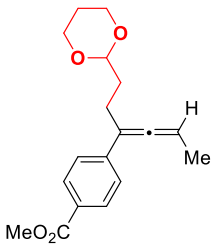
III-3c

From **III-1c** (81 mg, 0.2 mmol) and (1,3-dioxan-2-ylethyl)magnesium bromide solution in THF (0.22 mmol) following the general procedure described above, compound **III-3c** (58 mg, 0.19 mmol) was obtained in 93% yield as a pale yellow oil, after purification by flash column chromatography (hexane/AcOEt 95:5). ^{1}H NMR, ^{13}C NMR and MS data were consistent with literature values.[98]

[98] Soler-Yanes, R.; Arribas-Álvarez, I.; Guisán-Ceinos, M.; Buñuel, E.; Cárdenas, D. J. *Chem. Eur. J.* **2017**, *23*, 1584.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 (d, *J* = 8.6 Hz, 2H), 7.48 (d, *J* = 8.5 Hz, 2H), 5.56 (qt, *J* = 7.1, 3.3 Hz, 1H), 4.63 (t, *J* = 5.1 Hz, 1H), 4.19 – 4.07 (m, 2H), 3.83 – 3.73 (m, 2H), 2.58 – 2.44 (m, 2H), 2.19 – 2.04 (m, 1H), 1.90 – 1.80 (m, 2H), 1.77 (d, *J* = 7.1 Hz, 3H), 1.41 – 1.31 (m, 1H).

(±)-Methyl 4-(1-(1,3-dioxan-2-yl)hexa-3,4-dien-3-yl)benzoate, **III-3d**.

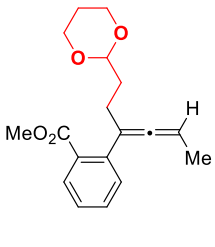


III-3d

From **III-1d** (79 mg, 0.2 mmol) and (1,3-dioxan-2-ylethyl)magnesium bromide solution in THF (0.22 mmol) following the general procedure described above, compound **III-3d** (54 mg, 0.17 mmol) was obtained in 89% yield as a pale yellow oil, after purification by flash column chromatography (pentane/Et_2O 90:10). ^{1}H NMR, ^{13}C NMR and MS data were consistent with literature values.[98]

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98 – 7.92 (m, 2H), 7.49 – 7.41 (m, 2H), 5.56 (qt, *J* = 7.0, 3.3 Hz, 1H), 4.63 (t, *J* = 5.1 Hz, 1H), 4.19 – 4.06 (m, 2H), 3.90 (s, 3H), 3.84 – 3.72 (m, 2H), 2.58 – 2.44 (m, 2H), 2.18 – 2.06 (m, 1H), 1.92 – 1.81 (m, 2H), 1.77 (d, *J* = 7.0 Hz, 3H), 1.40 – 1.30 (m, 1H).

(±)-Methyl 2-(1-(1,3-dioxan-2-yl)hexa-3,4-dien-3-yl)benzoate, **III-3e**.

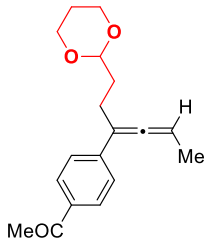


III-3e

From **III-1e** (79 mg, 0.2 mmol) and (1,3-dioxan-2-ylethyl)magnesium bromide solution in THF (0.22 mmol) following the general procedure described above, compound **III-3e** (30 mg, 0.10 mmol) was obtained in 50% yield as a pale yellow oil, after purification by flash column chromatography (pentane/Et_2O 90:10).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.45 – 7.37 (m, 1H), 7.33 – 7.26 (m, 2H), 5.25 (qt, *J* = 6.8, 3.2 Hz, 1H), 4.61 (t, *J* = 5.2 Hz, 1H), 4.14 – 4.05 (m, 2H), 3.86 (s, 3H), 3.81 – 3.69 (m, 2H), 2.46 – 2.35 (m, 2H), 2.14 – 2.00 (m, 1H), 1.85 – 1.77 (m, 2H), 1.66 (d, *J* = 7.0 Hz, 3H), 1.37 – 1.28 (m, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 203.2, 168.8, 139.5, 131.1, 130.8, 129.7, 129.28, 126.6, 104.5, 101.8, 87.8, 66.9, 52.0, 33.6, 27.7, 25.9, 14.3. **HRMS** (EI) calculated for $C_{18}H_{22}O_4$ $[M]^+$: 302.1518; Found: 302.1509.

(±)-1-(4-(1-(1,3-Dioxan-2-yl)hexa-3,4-dien-3-yl)phenyl)ethenone, **III-3f**.

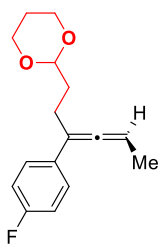


III-3f

From **III-1f** (76 mg, 0.2 mmol) and (1,3-dioxan-2-ylethyl)magnesium bromide solution in THF (0.22 mmol) following the general procedure described above (catalytic charge was changed to 0.02 mmol), compound **III-3f** (23 mg, 0.08 mmol) was obtained in 40% yield as a pale yellow oil, after purification by flash column chromatography (pentane/Et_2O 80:20). ^{1}H NMR, ^{13}C NMR and MS data were consistent with literature values.[¡Error! Marcador no definido.]

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92 – 7.85 (m, 2H), 7.51 – 7.45 (m, 2H), 5.57 (qt, *J* = 6.9, 3.2 Hz, 1H), 4.63 (t, *J* = 5.1 Hz, 1H), 4.17 – 4.06 (m, 2H), 3.85 – 3.71 (m, 2H), 2.58 (s, 3H), 2.56 – 2.46 (m, 2H), 2.19 – 2.01 (m, 1H), 1.90 – 1.80 (m, 2H), 1.77 (d, *J* = 7.1 Hz, 3H), 1.40 – 1.31 (m, 1H).

(–)-(*R*)-2-(3-(4-fluorophenyl)hexa-3,4-dien-1-yl)-1,3-dioxane, **(*R*)-III-3g**.

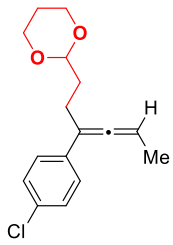


(*R*)-III-3g

From **(*R*)-III-1g** (71 mg, 0.2 mmol) and (1,3-dioxan-2-ylethyl)magnesium bromide solution in THF (0.22 mmol) following the general procedure described above, compound **(*R*)-III-3g** (50 mg, 0.19 mmol) was obtained in 95% yield as a pale yellow oil, after purification by flash column chromatography (pentane/Et_2O 97:3). From **III-1g,** following the same procedure without SPhos, compound **III-3g** (44 mg, 0.17 mmol) was obtained in 84% yield.

Compound **(*R*)-III-3g** was obtained in 97:3 enantiomeric ratio determined by SFC using Chiralpak-ID column [CO_2/MeOH (99:1)], 1.0 mL/min, τ_{major}= 18.7 min, τ_{minor}= 20.8 min. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.40 – 7.30 (m, 2H), 7.03 – 6.92 (m, 2H), 5.49 (qt, *J* = 6.9, 3.2 Hz, 1H), 4.62 (t, *J* = 5.1 Hz, 1H), 4.20 – 4.04 (m, 2H), 3.86 – 3.69 (m, 2H), 2.56 – 2.35 (m, 2H), 2.19 – 2.00 (m, 1H), 1.88 – 1.80 (m, 2H), 1.75 (d, *J* = 7.0 Hz, 3H), 1.40 – 1.30 (m, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 204.3 (d, $J_{C\text{-}F}$ = 2.0 Hz), 161.8 (d, $J_{C\text{-}F}$ = 245.4 Hz), 133.4 (d, $J_{C\text{-}F}$ = 3.2 Hz), 127.6 (d, $J_{C\text{-}F}$ = 7.9 Hz), 115.2 (d, $J_{C\text{-}F}$ = 21.4 Hz), 140.0, 101.9, 90.1, 67.1, 33.7, 26.0, 24.4, 14.5. **HRMS-(EI)** calculated for $C_{16}H_{18}FO_2$ $[M\text{-}H]^+$: 261.1291; Found: 261.0887. **$[\alpha]^{25}_D$**= –68.1 (*c* = 1.0, $CHCl_3$).

(±)-2-(3-(4-chlorophenyl)hexa-3,4-dien-1-yl)-1,3-dioxane, **III-3h**.

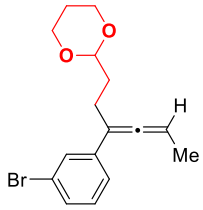


III-3h

From **III-1h** (74 mg, 0.2 mmol) and (1,3-dioxan-2-ylethyl)magnesium bromide solution in THF (0.22 mmol) following the general procedure described above, compound **III-3h** (50 mg, 0.18 mmol) was obtained in 90% yield as a pale yellow oil, after purification by flash column chromatography (cyclohexane/Et_2O 95:5). ^1H NMR, ^{13}C NMR and MS data were consistent with literature values.[98]

^1H NMR (300 MHz, $CDCl_3$) δ 7.35 – 7.28 (m, 2H), 7.28 – 7.22 (m, 2H), 5.50 (qt, *J* = 6.9, 3.6 Hz, 1H), 4.61 (t, *J* = 5.1 Hz, 1H), 4.17 – 4.07 (m, 2H), 3.83 – 3.71 (m, 2H), 2.54 – 2.39 (m, 2H), 2.20 – 2.03 (m, 1H), 1.89 – 1.79 (m, 2H), 1.75 (d, *J* = 7.0 Hz, 3H), 1.40 – 1.31 (m, 1H).

(±)-2-(3-(3-Bromophenyl)hexa-3,4-dien-1-yl)-1,3-dioxane, **III-3i**.



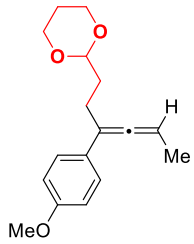
III-3i

From **III-1i** (83 mg, 0.2 mmol) and (1,3-dioxan-2-ylethyl)magnesium bromide solution in THF (0.22 mmol) following the general procedure described above, compound **III-3i** (58 mg, 0.18 mmol) was obtained in 90% yield as a pale yellow oil, after purification by flash column chromatography (pentane/Et_2O 95:5).

^1H NMR (300 MHz, $CDCl_3$) δ 7.52 (t, *J* = 1.9 Hz, 1H), 7.30 (ddt, *J* = 8.0, 5.1, 1.3 Hz, 2H), 7.15 (t, *J* = 7.9 Hz, 1H), 5.53 (qt, *J* = 7.0, 3.3 Hz, 1H), 4.61 (t, *J* = 5.2 Hz, 1H), 4.19 – 4.07 (m, 2H), 3.84 – 3.71 (m, 2H), 2.55 – 2.36 (m, 2H), 2.19 – 2.02 (m, 1H), 1.88 – 1.79 (m, 2H), 1.76 (d, *J* = 7.0 Hz, 3H), 1.40 – 1.30 (m, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 204.7, 140.0, 129.8, 129.4, 129.1, 124.6, 122.7, 104.0, 102.0, 90.5, 67.1, 33.7, 26.0, 24.0,

14.4. **HRMS** (EI) calculated for $C_{16}H_{19}BrO_2$ $[M]^+$: 322.0568; Found: 322.0552.

(±)-2-(3-(4-Methoxyphenyl)hexa-3,4-dien-1-yl)-1,3-dioxane, **III-3j**.

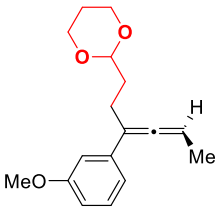


III-3j

From **III-1j** (74 mg, 0.2 mmol) and (1,3-dioxan-2-ylethyl)magnesium bromide solution in THF (0.22 mmol), following the general procedure described above, compound **III-3j** (33 mg, 0.12 mmol) was obtained in 60% yield as a pale yellow oil, after purification by flash column chromatography (pentane/Et_2O 97:3).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 – 7.29 (m, 2H), 6.88 – 6.82 (m, 2H), 5.53 – 5.41 (m, 1H), 4.62 (t, *J* = 5.2 Hz, 1H), 4.19 – 4.06 (m, 2H), 3.81 – 3.71 (m, 2H), 3.80 (s, 3H), 2.51 – 2.42 (m, 2H), 2.16 – 2.03 (m, 1H), 1.89 – 1.80 (m, 2H), 1.74 (d, *J* = 7.0 Hz, 3H), 1.38 – 1.31 (m, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 204.0, 158.5, 129.8, 127.2, 113.9, 104.3, 102.1, 89.7, 67.1, 55.4, 33.8, 26.0, 24.4, 14.7. **HRMS-(EI)** calculated for $C_{17}H_{21}O_3$ $[M]^+$: 274.1491; Found 274.1495.

(–)-(*R*)-2-(3-(3-methoxyphenyl)hexa-3,4-dien-1-yl)-1,3-dioxane, **(*R*)-III-3k**.



(*R*)-III-3k

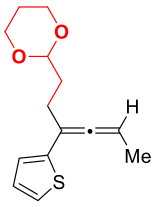
From **(*R*)-III-1k** (74 mg, 0.2 mmol) and (1,3-dioxan-2-ylethyl)magnesium bromide solution in THF (0.22 mmol) following the general procedure described above, compound **(*R*)-III-3k** (51 mg, 0.19 mmol) was obtained in 93% yield as a pale yellow oil, after purification by flash column chromatography (pentane/Et_2O 97:3). From **III-1k,** following the same

procedure without SPhos, compound **III-3k** (51 mg, 0.19 mmol) was obtained in 93% yield.

^{1}H NMR, ^{13}C NMR and MS data for **III-3k** were consistent with literature values.[98] **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.25 – 7.19 (m, 1H), 7.07 – 6.90 (m, 2H), 6.77 – 6.71 (m, 1H), 5.49 (qt, *J* = 6.9, 3.3 Hz, 1H), 4.62 (t, *J* = 5.2 Hz, 1H), 4.17 – 4.08 (m, 2H), 3.82 – 3.72 (m, 2H), 3.80 (s, 3H), 2.55 – 2.41 (m, 2H), 2.19 – 2.02 (m, 1H), 1.90 – 1.80 (m, 2H), 1.75 (d, *J* = 7.0 Hz, 3H), 1.39 – 1.30 (m, 1H).

Compound **(*R*)-III-3k** was obtained in 98:2 enantiomeric ratio determined by SFC using Chiralpak-IA column [CO_2/MeOH (99:1)], 1.0 mL/min, τ_{major}= 25.5 min, τ_{minor}= 27.3 min. **$[\alpha]^{25}_{D}$**= –66.7 (*c* = 1.0, $CHCl_3$).

(±)-2-(3-(Thiophen-2-yl)hexa-3,4-dien-1-yl)-1,3-dioxane, **III-3l**.

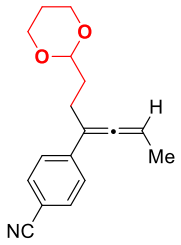


III-3l

From **III-1l** (69 mg, 0.2 mmol) and (1,3-dioxan-2-ylethyl)magnesium bromide solution in THF (0.22 mmol) following the general procedure described above, compound **III-3l** (40 mg, 0.16 mmol) was obtained in 80% yield as a pale yellow oil, after purification by flash column chromatography (cyclohexane/EtOAc 95:5).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.13 (dd, *J* = 5.0, 1.4 Hz, 1H), 7.00 – 6.90 (m, 2H), 5.51 (qt, *J* = 6.9, 3.2 Hz, 1H), 4.62 (t, *J* = 5.2 Hz, 1H), 4.18 – 4.09 (m, 2H), 3.83 – 3.73 (m, 2H), 2.54 – 2.44 (m, 2H), 2.16 – 2.03 (m, 1H), 1.91 – 1.82 (m, 2H), 1.72 (d, *J* = 3.3 Hz, 3H), 1.40 – 1.31 (m, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 203.4, 143.0, 127.4, 124.1, 122.7, 101.9, 100.8, 90.6, 67.1, 33.6, 26.0, 25.5, 14.6. **HRMS** (EI) calculated for $C_{14}H_{17}O_2S$ [M-H]$^{+}$: 249.0949; Found: 249.0553.

(±)-4-(1-(1,3-Dioxan-2-yl)hexa-3,4-dien-3-yl)benzonitrile, **III-3m**.

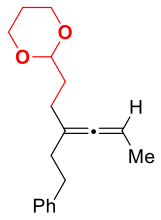


III-3m

From **III-1m** (72 mg, 0.2 mmol) and (1,3-dioxan-2-ylethyl)magnesium bromide solution in THF (0.22 mmol) following the general procedure described above, compound **III-3m** (45 mg, 0.17 mmol) was obtained in 84% yield as a pale yellow oil, after purification by flash column chromatography (pentane/Et_2O 90:10). ^{1}H NMR, ^{13}C NMR and MS data were consistent with literature values.[98]

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61 – 7.52 (m, 2H), 7.50 – 7.41 (m, 2H), 5.58 (qt, *J* = 7.1, 3.3 Hz, 1H), 4.62 (t, *J* = 5.1 Hz, 1H), 4.19 – 4.06 (m, 2H), 3.84 – 3.69 (m, 2H), 2.54 – 2.41 (m, 2H), 2.19 – 2.02 (m, 1H), 1.88 – 1.79 (m, 2H), 1.77 (d, *J* = 7.0 Hz, 3H) 1.41 – 1.31 (m, 1H).

(±)-2-(3-Phenethylhexa-3,4-dien-1-yl)-1,3-dioxane, **III-3n**.

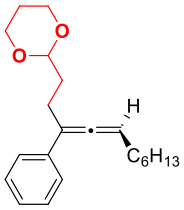


III-3n

From **III-1n** (73 mg, 0.2 mmol) and (1,3-dioxan-2-ylethyl)magnesium bromide solution in THF (0.22 mmol) following the general procedure described above (temperature was changed to rt), compound **III-3n** (33 mg, 0.12 mmol) was obtained in 61% yield as a pale yellow oil, after purification by flash column chromatography (cyclohexane/EtOAc 95:5).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 – 7.24 (m, 2H), 7.22 – 7.13 (m, 3H), 5.08 (qt, *J* = 7.8, 3.4, 1H), 4.54 (t, *J* = 5.2 Hz, 1H), 4.16 – 4.05 (m, 2H), 3.82 – 3.68 (m, 2H), 2.77 – 2.66 (m, 2H), 2.29 – 2.18 (m, 2H), 2.15 – 1.99 (m, 3H), 1.79 – 1.68 (m, 2H), 1.55 (d, *J* = 7.1 Hz, 3H), 1.39 – 1.29 (m, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 201.7, 142.5, 128.5, 128.31, 125.8, 102.8, 102.1, 87.9, 67.1, 34.7, 34.2, 33.4, 27.0, 26.0, 15.0. **HRMS** (ESI) calculated for $C_{18}H_{24}NaO_2$ $[M+Na]^+$: 295.1674; Found: 295.1665.

(–)-(*R*)-2-(3-Phenylundeca-3,4-dien-1-yl)-1,3-dioxane **III-3o**.

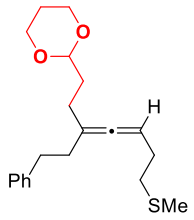


(*R*)-III-3o

From **(*R*)-III-1o** (82 mg, 0.2 mmol) and (1,3-dioxan-2-ylethyl)magnesium bromide solution in THF (0.22 mmol) following the general procedure described above, compound **(*R*)-III-3o** (48 mg, 0.15 mmol) was obtained in 76% yield as a pale yellow oil, after purification by flash column chromatography (pentane/Et_2O 95:5). From **III-1o,** following the same procedure without SPhos, compound **III-3o** (51 mg, 0.16 mmol) was obtained in 81% yield.

Compound **(*R*)-III-3o** was obtained in 98:2 enantiomeric ratio determined by SFC using Chiralpak-IB column [CO_2/MeOH (99:1)], 1.0 mL/min, τ_{major}= 28.3 min, τ_{minor}= 27.7 min. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.45 – 7.38 (m, 2H), 7.33 – 7.27 (m, 2H), 7.21 – 7.13 (m, 1H), 5.53 (tt, *J* = 6.6, 3.3 Hz, 1H), 4.63 (t, *J* = 5.2 Hz, 1H), 4.20 – 4.05 (m, 2H), 3.83 – 3.68 (m, 2H), 2.57 – 2.45 (m, 2H), 2.16 – 2.06 (m, 3H), 1.92 – 1.81 (m, 2H), 1.56 – 1.21 (m, 10H), 0.96 – 0.82 (m, 3H). **^{13}C NMR** (76 MHz, $CDCl_3$) δ 203.6, 137.6, 128.4, 126.5, 126.0, 105.2, 102.1, 95.5, 67.1, 33.8, 31.8, 29.4, 29.3, 29.1, 26.0, 24.2, 22.8, 14.2. **HRMS** (EI) calculated for $C_{21}H_{30}O_2$ $[M]^+$: 314.2246; Found: 314.2223. **$[\alpha]^{25}_D$**= –78.2 (*c* = 1.0, $CHCl_3$).

(±)-2-(7-(Methylthio)-3-phenethylhepta-3,4-dien-1-yl)-1,3-dioxane, **III-3p**.

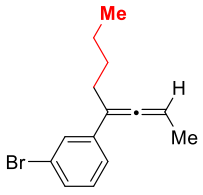


III-3p

From **III-1p** (85 mg, 0.2 mmol) and (1,3-dioxan-2-ylethyl)magnesium bromide solution in THF (0.22 mmol) following the general procedure described above (temperature was changed to rt), compound **III-3p** (48 mg, 0.14 mmol) was obtained in 72% yield as a pale yellow oil, after purification by flash column chromatography (cyclohexane/EtOAc 90:10).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 – 7.22 (m, 2H), 7.22 – 7.13 (m, 3H), 5.18 (qt, *J* = 6.2, 3.1 Hz, 1H), 4.54 (t, *J* = 5.1 Hz, 1H), 4.15 – 4.05 (m, 2H), 3.83 – 3.67 (m, 2H), 2.74 (t, *J* = 7.9 Hz, 2H), 2.51 – 2.41 (m, 2H), 2.32 – 2.01 (m, 10H), 1.79 – 1.68 (m, 2H), 1.38 – 1.29 (m, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 201.0, 142.2, 128.5, 128.3, 125.8, 104.4, 102.0, 91.8, 67.0, 34.6, 34.1, 33.8, 33.4, 29.3, 26.9, 26.0, 15.69. **HRMS** (EI) calculated for $C_{20}H_{28}O_2S$ $[M]^+$: 332.1810; Found: 332.1797.

(±)-1-Bromo-3-(octa-2,3-dien-4-yl)benzene, **III-3q**.



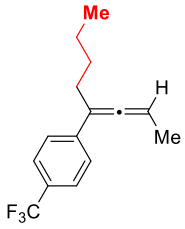
III-3q

From **III-1i** (83 mg, 0.2 mmol) and *n*-butylmagnesium chloride solution in THF (0.22 mmol) following the general procedure described above, compound **III-3q** (30 mg, 0.11 mmol) was obtained in 57% yield as a pale yellow oil, after purification by flash column chromatography (hexane/Et_2O 98:2).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 (t, *J* = 1.8 Hz, 1H), 7.34 – 7.27 (m, 2H), 7.16 (dd, *J* = 8.3, 7.4 Hz, 1H), 5.49 (qt, *J* = 6.9, 3.1 Hz, 1H), 2.41 – 2.31 (m, 2H), 1.76 (d, *J* = 0.7 Hz, 3H), 1.58 – 1.34 (m, 4H), 0.93 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 205.0, 140.3, 129.8, 129.3, 129.2,

124.6, 122.7, 104.3, 89.5, 30.1, 29.6, 22.5, 14.4, 14.1. **HRMS** (EI) calculated for $C_{14}H_{17}Br$ $[M]^+$: 264.0514; Found: 264.0478.

(±)-1-(Octa-2,3-dien-4-yl)-4-(trifluoromethyl)benzene, **III-3r**.

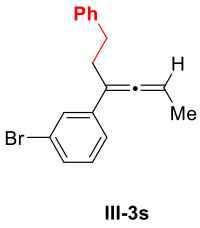


III-3r

From **III-1c** (81 mg, 0.2 mmol) and *n*-butylmagnesium bromide chloride solution in THF (0.22 mmol) following the general procedure described above, compound **III-3r** (42 mg, 0.17 mmol) was obtained in 83% yield as a pale yellow oil, after purification by flash column chromatography (pentane /Et_2O 98:2).

^{1}H NMR (300 MHz, CDCl3) δ 7.54 (d, *J* = 8.4 Hz, 2H), 7.48 (d, *J* = 8.4 Hz, 2H), 5.52 (qt, *J* = 6.8, 3.1 Hz, 1H), 2.45 – 2.35 (m, 2H), 1.78 (d, *J* = 7.0 Hz, 3H), 1.58 – 1.35 (m, 5H), 0.94 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 205.6, 141.7, 128.4 (q, $J_{C\text{-}F}$ = 32.4 Hz), 126.3, 125.3 (q, $J_{C\text{-}F}$ = 3.9 Hz), 124.5 (q, $J_{C\text{-}F}$ = 270.3 Hz), 104.5, 89.6, 30.2, 29.6, 22.5, 14.3, 14.1. **HRMS** (EI) calculated for $C_{15}H_{17}F_3$ $[M]^+$: 254.1282; Found: 254.1279.

(±)-1-Bromo-3-(1-phenylhexa-3,4-dien-3-yl)benzene, **III-3s**.

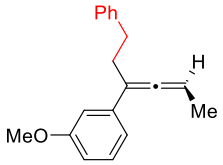


III-3s

From **III-3i** (83 mg, 0.2 mmol) and phenethylmagnesium bromide solution in THF (0.22 mmol) following the general procedure described above, compound **III-3s** (55 mg, 0.18 mmol) was obtained in 88% yield as a pale yellow oil, after purification by flash column chromatography (hexane/Et_2O 98:2).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 (t, *J* = 1.9 Hz, 1H), 7.34 – 7.27 (m, 4H), 7.24 – 7.14 (m, 4H), 5.51 (qt, *J* = 6.9, 3.1 Hz, 1H), 2.88 – 2.79 (m, 2H), 2.74 – 2.59 (m, 2H), 1.69 (d, *J* = 7.0 Hz, 3H). **^{13}C NMR** (76 MHz, $CDCl_3$) δ 205.1, 142.0, 139.9, 129.9, 129.5, 129.1, 128.6, 128.5, 126.0, 124.6, 122.8, 103.8, 90.3, 34.2, 31.7, 14.3. **HRMS** (EI) calculated for $C_{18}H_{17}Br$ $[M]^+$: 312.0514; Found: 312.0485.

(–)-(*R*)-1-Methoxy-3-(2-methylhexa-3,4-dien-3-yl)benzene, **(*R*)-III-3t**.

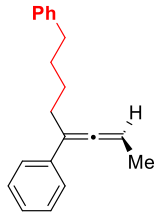


(*R*)-III-3t

From **(*R*)-III-1k** (75 mg, 0.2 mmol) and phenethylmagnesium bromide solution in THF (0.22 mmol) following the general procedure described above, compound **(*R*)-III-3t** (50 mg, 0.19 mmol) was obtained in 95% yield as a pale yellow oil, after purification by flash column chromatography (pentane/Et_2O 95:5). From **III-1k,** following the same procedure without SPhos, compound **III-3t** (52 mg, 0.20 mmol) was obtained in 97% yield.

Compound **(*R*)-III-3t** was obtained in 96:4 enantiomeric ratio determined by SFC using Chiralpak-IB column [CO_2/MeOH (99:1)], 1 mL/min, τ_{major}= 25.4 min, τ_{minor}= 30.8 min. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.26 – 7.08 (m, 7H), 6.96 – 6.87 (m, 2H), 6.68 (ddd, *J* = 8.2, 2.5, 1.1 Hz, 1H), 5.39 (qt, *J* = 6.9, 3.0 Hz, 1H), 3.73 (d, *J* = 1.1 Hz, 3H), 2.77 (dd, *J* = 8.2, 5.8 Hz, 2H), 2.69 – 2.57 (m, 2H), 1.61 (dd, J = 7.1, 1.1 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 205.0, 159.9, 142.3, 139.1, 129.4, 128.7, 128.4, 125.9, 118.7, 112.1, 111.9, 104.7, 89.7, 55.4, 34.4, 31.9, 14.4. **HRMS** (EI) calculated for $C_{19}H_{20}O$ $[M]^+$: 264.1514; Found: 264.1481. **$[\alpha]^{25}_D$**= –52.0 (*c* = 1.0, $CHCl_3$).

(–)-(*R*)-Octa-5,6-diene-1,5-diyldibenzene, **(*R*)-III-3u**.

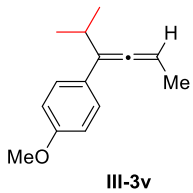


(*R*)-III-3u

From **(*R*)-III-1a** (75 mg, 0.2 mmol) and (4-phenylbutyl)magnesium bromide solution in THF (0.22 mmol) following the general procedure described above, compound **(*R*)-III-3u** (47 mg, 0.18 mmol) was obtained in 90% yield as a pale-yellow oil, after purification by flash column chromatography (hexanes). From **III-1a,** following the same procedure, compound **III-3u** (46 mg, 0.18 mmol) was obtained in 88% yield.

Compound **(*R*)-III-3u** was obtained in 98:2 enantiomeric ratio determined by SFC using Chiralpak-ID column [CO_2/MeOH (99:1)], 1 mL/min, τ_{major}= 11.3 min, τ_{minor}= 12.9 min. ^{1}H NMR, ^{13}C NMR and MS data were consistent with literature values.[99] **^{1}H NMR** (300 MHz, Chloroform-d) δ 7.44 – 7.38 (m, 2H), 7.36 – 7.25 (m, 4H), 7.22 – 7.18 (m, 4H), 5.48 (qt, J = 6.8, 3.0 Hz, 1H), 2.73 – 2.63 (m, 2H), 2.54 – 2.41 (m, 2H), 1.78 (d, J = 4.8 Hz, 3H), 1.75 – 1.58 (m, 4H). **$[\alpha]^{25}_D$**= –54.0 (*c* = 1.0, $CHCl_3$).

(±)-1-Methoxy-4-(2-methylhexa-3,4-dien-3-yl)benzene, **III-3v**.



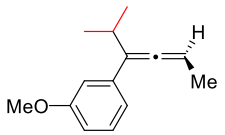
III-3v

From **III-1j** (75 mg, 0.2 mmol) and isopropylmagnesium bromide solution in THF (0.22 mmol) following the general procedure described above, compound **III-3v** (40 mg, 0.20 mmol) was obtained in 98% yield as a pale-yellow oil, after purification by flash column chromatography (cyclohexane/EtOAc 95:5).

[99] Uehling, M.R.; Marionni, S.T.; Lalic, G. *Org. Lett.*, **2012**, *14*, 362.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 – 7.28 (m, 2H), 6.91 – 6.83 (m, 2H), 5.47 (qd, *J* = 6.9, 2.4 Hz, 1H), 3.81 (s, 3H), 2.87 – 2.66 (m, 1H), 1.76 (dd, *J* = 6.9, 0.7 Hz, 3H), 1.13 (d, *J* = 5.8 Hz, 3H), 1.10 (d, *J* = 5.6 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 203.4, 158.4, 129.9, 127.7, 113.9, 112.1, 89.8, 55.4, 28.2, 22.7, 22.3, 14.8. **HRMS** (EI) calculated for $C_{14}H_{18}O$ $[M]^+$: 202.1358; Found: 202.1354.

(–)-(*R*)-1-Methoxy-3-(1-phenylhexa-3,4-dien-3-yl)benzene, **(*R*)-III-3w**.

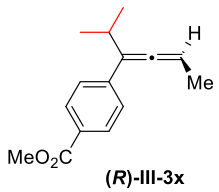


(*R*)-III-3w

From **(*R*)-III-1k** (75 mg, 0.2 mmol) and isopropylmagnesium bromide solution in THF (0.22 mmol) following the general procedure described above, compound **(*R*)-III-3w** (33 mg, 0.16 mmol) was obtained in 82% yield as a pale yellow oil, after purification by flash column chromatography (pentane/Et_2O 95:5). From **III-1k**, following the same procedure, compound **III-3w** (29 mg, 0.14 mmol) was obtained in 71% yield.

Compound **(*R*)-III-3w** was obtained in 97:3 enantiomeric ratio determined by SFC using Chiralpak-IB column [CO_2/MeOH (99.5:0.5)], 0.5 mL/min, τ_{major}= 26.3 min, τ_{minor}= 24.5 min. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.23 (t, *J* = 7.8 Hz, 1H), 7.02 – 6.97 (m, 1H), 6.97 – 6.94 (m, 1H), 6.78 – 6.72 (m, 1H), 5.49 (qd, *J* = 6.9, 2.3 Hz, 1H), 3.81 (s, 3H), 2.79 (pd, *J* = 6.7, 2.3 Hz, 1H), 1.76 (d, *J* = 6.9 Hz, 3H), 1.13 (d, *J* = 5.3 Hz, 3H), 1.11 (d, *J* = 5.2 Hz, 3H). **^{13}C NMR** (75 MHz, CDCl3) δ 203.9, 159.8, 139.3, 129.3, 119.2, 112.7, 112.6, 111.6, 90.0, 55.3, 28.1, 22.7, 22.4, 14.6. **HRMS** (EI) calculated for $C_{14}H_{19}O$ $[M+H]^+$: 204.1436; Found: 204.1427. **$[\alpha]^{25}_D$**= –47.6 (*c* = 1.0, $CHCl_3$)

(–)-(*R*)-Methyl 4-(2-methylhexa-3,4-dien-3-yl)benzoate, **(*R*)-III-3x**.



(*R*)-III-3x

From **(*R*)-III-1d** (79 mg, 0.2 mmol) and isopropylmagnesium bromide solution in THF (0.22 mmol) following the general procedure described above, compound **(*R*)-III-3x** (39 mg, 0.17 mmol) was obtained in 85% yield as a pale yellow oil, after purification by flash column chromatography (pentane/Et_2O 97:3). From **III-1d,** following the same procedure without SPhos, compound **III-3x** (44 mg, 0.19 mmol) was obtained in 95% yield.

Compound **(*R*)-III-3x** was obtained in 97:3 enantiomeric ratio determined by SFC using Chiralpak-ID column [CO_2/MeOH (99:1)], 1 mL/min, τ_{major}= 14.4 min, τ_{minor}= 14.0 min.

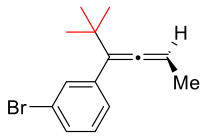
Using isopropylmagnesium chloride solution in THF (0.22 mmol) compound **(*R*)-III-3x** (41 mg, 0.18 mmol) was obtained in 89% yield and 97:3 enantiomeric ratio as a pale yellow oil, after purification by flash column chromatography (pentane/Et_2O 97:3).

Using isopropylmagnesium chloride solution in Et_2O (0.22 mmol) compound **(*R*)-III-3x** (12 mg, 0.05 mmol) was obtained in 26% yield and 90:10 enantiomeric ratio as a pale yellow oil, after purification by flash column chromatography (pentane/Et_2O 97:3). The low yield is attributed to the low solubility of the starting material in Et_2O.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 – 7.89 (m, 2H), 7.49 – 7.38 (m, 2H), 5.55 (qd, *J* = 7.0, 2.4 Hz, 1H), 3.90 (s, 3H), 2.82 (septd, *J* = 6.7, 2.4 Hz, 1H), 1.78 (d, *J* = 7.0 Hz, 3H), 1.13 (d, *J* = 6.7 Hz, 3H), 1.11 (d, *J* = 6.7 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 204.8, 167.2, 142.6, 129.7, 127.9, 126.4, 112.3, 90.6, 52.1, 27.8, 22.6, 22.3, 14.4. **HRMS** (ESI)

calculated for $C_{15}H_{18}NaO_2$ $[M+Na]^+$: 253.1204; Found: 253.1198. **[α]$^{25}_D$**= –83.7 (*c* = 1.0, $CHCl_3$).

(–)-(*R*)-1-bromo-3-(2,2-dimethylhexa-3,4-dien-3-yl)benzene **(*R*)-III-3y**.

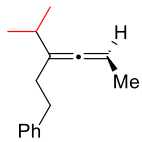


(*R*)-III-3y

From **(*R*)-III-1i** (83 mg, 0.2 mmol) and *tert*-butylmagnesium chloride solution in THF (0.22 mmol) following the general procedure described above, compound **(*R*)-III-3y** (43 mg, 0.16 mmol) was obtained in 81% yield as a pale yellow oil, after purification by flash column chromatography (pentane/Et_2O 97:3). From **III-1i,** following the same procedure, compound **III-3y** (38 mg, 0.14 mmol) was obtained in 72% yield.

Compound **(*R*)-III-3x** was obtained in 98:2 enantiomeric ratio determined by GC on a Chirasil Dex-CB column (60 ºC, hold 3 min, 60→120 °C @ 10 °C/min, hold 2 min, then →160 °C @ 0.5 °C/min, then →180 °C @ 10 °C/min; flow rate 1.0 mL/min.). τ_{major}= 27.6 min, τ_{minor}= 27.9 min. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.52 – 7.30 (m, 2H), 7.22 – 7.07 (m, 2H), 5.20 (q, J = 6.9 Hz, 1H), 1.69 (d, J = 6.9 Hz, 3H), 1.12 (s, 9H). **^{13}C NMR** (75 MHz, CDCl3) δ 202.6, 140.6, 132.4, 129.5, 129.3, 128.1, 121.8, 114.1, 86.8, 34.3, 30.0, 14.8. **HRMS** (APCI) calculated for $C_{14}H_{18}Br$ $[M+H]^+$: 265.0586; Found: 265.0585. **[α]$^{25}_D$**= –22.3 (*c* = 1.0, $CHCl_3$).

(–)-(*S*)-(3-isopropylhexa-3,4-dien-1-yl)benzene, **(*S*)-III-3z**.



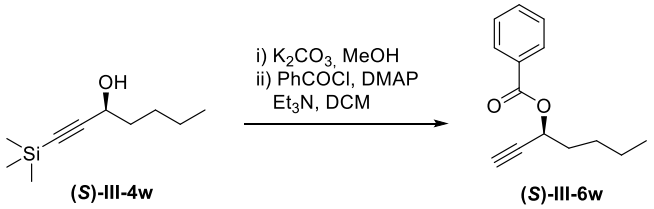
(*S*)-III-3z

From **(*R*)-III-1n** (73 mg, 0.2 mmol) and isopropylmagnesium chloride solution in THF (0.22 mmol) following the general procedure described above, compound **(*S*)-III-3z** (35 mg, 0.18 mmol) was obtained in 88% yield as a pale yellow oil, after purification by flash column chromatography (pentane/Et_2O 97:3). From **III-1n,** following the same procedure, compound **III-3z** (33 mg, 0.17 mmol) was obtained in 83% yield.

Compound **(*S*)-III-3z** was obtained in 98:2 enantiomeric ratio determined by GC on a Chirasil Dex-CB column (60 ºC, hold 3 min, then 60→80 °C @ 10 °C/min, hold 2 min, then →140 °C @ 0.5 °C/min, then →180 °C @ 10 °C/min, hold 3 min; flow rate 1.0 mL/min.). τ_{major}= 68.5 min, τ_{minor}= 70.1 min. **^{1}H NMR** (300 MHz, $CDCl_3$) δ7.24 – 7.04 (m, 5H), 5.14 – 4.98 (m, 1H), 2.70 – 2.58 (m, 2H), 2.23 – 2.12 (m, 2H), 2.10 – 1.92 (m, 1H), 1.52 (d, J = 6.8 Hz, 3H), 0.93 (dd, J = 6.8, 1.5 Hz, 6H). **^{13}C NMR** (75 MHz, CDCl3) δ 200.9, 142.8, 128.6, 128.3, 125.8, 110.0, 88.3, 34.5, 32.7, 31.4, 22.0, 21.9, 15.2. **HRMS** (EI) calculated for $C_{15}H_{20}$ $[M]^+$: 200.1565; Found: 200.1556. **$[\alpha]^{25}_D$**= –8.4 (*c* = 1.0, $CHCl_3$).

3.6.5. Derivatizations to determine the enantiomeric excess of **(*S*)-III-4w**, **(*R*)-III-2x** and **(*R*)-III-2y**.

*3.6.5.1. Synthesis of (–)-(S)-hept-1-yn-3-yl benzoate, **(S)-III-6w**.*



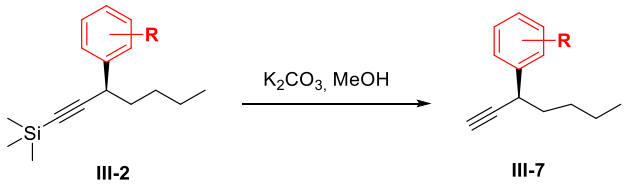
(*S*)-III-4w **(*S*)-III-6w**

K_2CO_3 (1.2 equiv) was added to a solution of **(*S*)-III-4w** (79 mg, 0.43 mmol, 1 equiv) in MeOH/DCM (8:1, 4.5 mL). The reaction mixture was stirred overnight at room temperature and then quenched with H_2O and extracted with DCM (x3). The combined organic phases were washed with brine, dried over Na_2SO_4, filtered and concentrated under vacuum to afford the terminal alkyne. The crude product was used in the next step without further purification.

To a solution of crude product in CH_2Cl_2 (2 mL), 4-dimethylaminopyridine (DMAP) (110 mg, 0.9 mmol, 2.1 equiv), triethylamine (180 µL, 1.3 mmol, 3 equiv) and benzoyl chloride (100 µL, 0.86 mmol, 2.0 equiv) were added. The reaction mixture was stirred for 2 h at room temperature and then quenched with H_2O. The aqueous layer was extracted with Et_2O (x3) and the combined organic phases were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography over silica gel using hexane/EtOAc, 95:5 as eluent. Compound **(*S*)-III-6w** (74 mg, 0.34 mmol) was obtained in 82% global yield as a colorless oil.

Compound **(*S*)-III-6w** was obtained in 93:7 enantiomeric ratio determined by SFC using Chiralpak-IA column [CO_2/MeOH (99.5:0.5)], 0.5 mL/min, τ_{major}= 27.1 min, τ_{minor}= 24.9 min. $[\alpha]^{20}_D$= -26.7 (*c* = 1.0, $CHCl_3$). ^{1}H NMR, ^{13}C NMR and MS data were consistent with literature values.[100] **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.12 – 8.01 (m, 2H), 7.62 – 7.52 (m, 1H), 7.49 – 7.40 (m, 2H), 5.60 (td, *J* = 6.6, 2.1 Hz, 1H), 2.49 (d, *J* = 2.1 Hz, 1H), 1.98 – 1.87 (m, 2H), 1.58 – 1.47 (m, 2H), 1.42 – 1.31 (m, 2H), 0.94 (t, *J* = 7.2 Hz, 3H).

3.6.5.2. General procedure for the deprotection of silylated alkynes

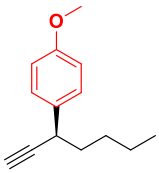


III-2 III-7

K_2CO_3 (1.2 equiv) was added to a solution of the corresponding TMS-protected alkyne (1 equiv) in MeOH/DCM (8:1, 1 mL/mmol of alkyne). The reaction mixture was stirred overnight at room temperature and then quenched with H_2O and extracted with DCM (x3). The combined organic phases were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography over silica gel using hex/EtOAc, 98:2 as eluent.

[100] Nakamura, K.; Takenaka, K. *Tetrahedron: Asymmetry*, **2002**, *13*, 415.

(+)-(*S*)-1-(Hept-1-yn-3-yl)-4-methoxybenzene, **(*S*)-III-7x**.

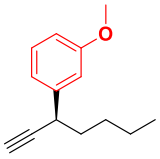


(*S*)-III-7x

From **(*R*)-III-2x** (29 mg, 0.11 mmol) following the general procedure described above, compound **(*S*)-III-7x** (20 mg, 0.10 mmol) was obtained in 89% yield as a yellow oil.

Compound **(*S*)-III-7x** was obtained in 91:9 enantiomeric ratio determined by SFC using Chiralpak-IA column [CO_2/MeOH (99.8:0.2)], 0.5 mL/min, τ_{major}= 26.3 min, τ_{minor}= 24.6 min. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.28 (d, *J* = 8.7 Hz, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 3.80 (s, 3H), 3.61 – 3.54 (m, 1H), 2.25 (d, *J* = 2.5 Hz, 1H), 1.80 – 1.68 (m, 2H), 1.47 – 1.28 (m, 4H), 0.90 (t, *J* = 7.0 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 158.5, 134.0, 128.4, 114.0, 86.7, 70.6, 55.4, 38.2, 36.9, 29.5, 22.5, 14.1. **[α]$^{20}_D$**= +15.9 (*c* = 1.0, $CHCl_3$). **HRMS-EI$^+$** m/z calculated for $C_{14}H_{19}O$ $[M+H]^+$: 203.1430, found 203.1425.

(+)-(*S*)-1-(Hept-1-yn-3-yl)-3-methoxybenzene, **(*S*)-III-7y**.

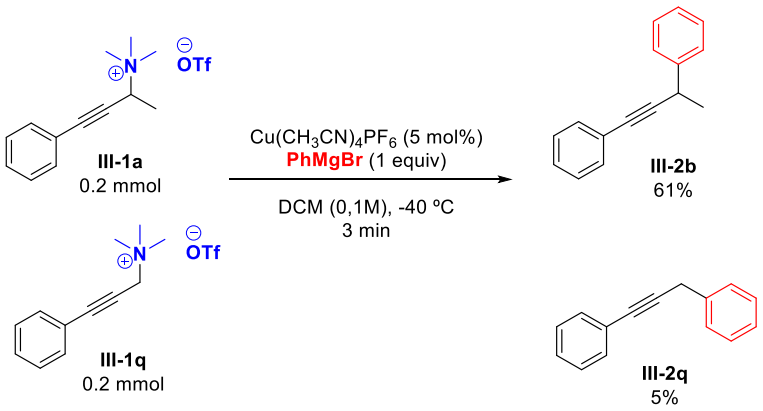


(*S*)-III-7y

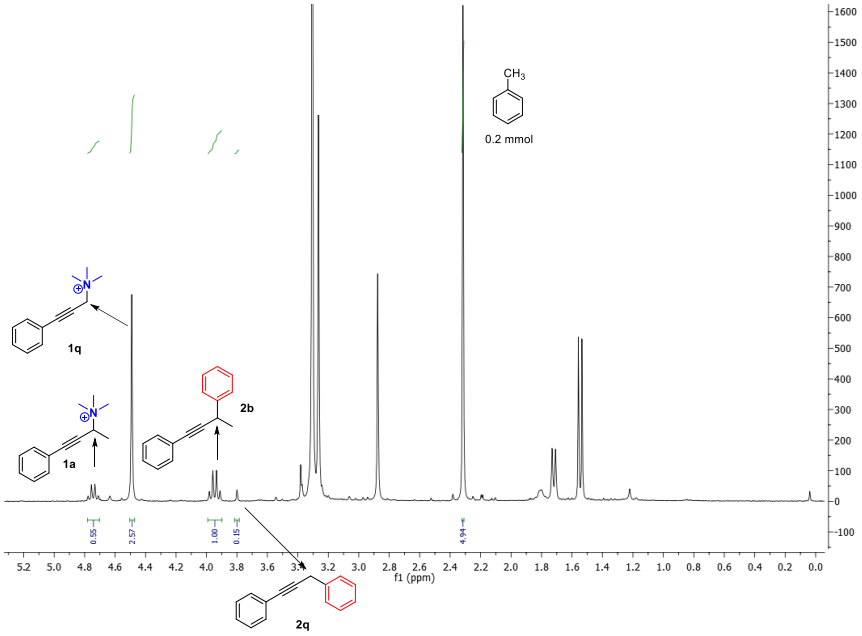
From **(*R*)-III-2y** (51 mg, 0.18 mmol) following the general procedure described above, compound **(*S*)-III-7y** (32 mg, 0.16 mmol) was obtained in 87% yield as a yellow oil.

Compound **(*S*)-III-7y** was obtained in 92:8 enantiomeric ratio determined by SFC using Chiralpak-IA column [CO_2/MeOH (99.8:0.2)], 0.5 mL/min, τ_{major}= 27.1 min, τ_{minor}= 25.3 min. **^{1}H NMR** (300 MHz, $CDCl_3$) 7.24 (m, 1H), 6.94 (m, 2H), 6.82 – 6.75 (m, 1H), 3.82 (s, 3H), 3.63 – 3.55 (m, 1H), 2.26 (d, *J* = 2.5 Hz, 1H), 1.76 (m, 2H), 1.51 – 1.28 (m, 4H), 0.89 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 159.9, 143.5, 129.6, 119.9, 113.4, 112.1, 86.2, 71.0, 55.4, 38.1, 37.7, 29.6, 22.5, 14.1. **[α]$^{20}_D$**= +18.2 (*c* = 1.0, $CHCl_3$). **HRMS-EI$^+$** m/z calculated for $C_{14}H_{19}O$ $[M+H]^+$: 202.1430 found 203.1429.

3.6.6. Competition experiment.



An oven-dried vial was charged with $[Cu(CH_3CN)_4]PF_6$ (3.8 mg, 0.01 mmol) and both primary (0.2 mmol) and secondary ammonium salt (0.2 mmol) and was sealed with a septum. The vial was connected to an argon-vacuum line, evacuated and backfilled with argon (x3). CH_2Cl_2 (2 mL) was added and the mixture was stirred for 5 min at room temperature. The reaction mixture was cooled to –40 ºC and phenyl magnesium bromide solution in THF (0.76 M, 0.2 mmol) was added dropwise. The mixture was stirred at –40 ºC for 3 minutes. Water (0.1 mL) was added and the solution was filtered through a short pad of $MgSO_4$ and rinsed with CH_2Cl_2. The solvent was removed under reduced pressure and toluene was added as internal standard. The ^{1}H-NMR of the crude product showed compounds **III-2a** (65% yield) and **III-2q** (5% yield) and unreacted starting materials.

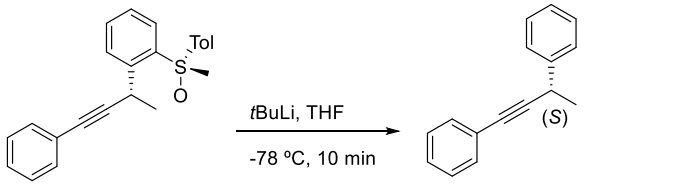


3.6.7. Assignment of the Absolute Configuration.

The absolute configuration was stablished for compounds ***(R)*-III-2b**, **(*R*)-III-2w**, **(*R*)-III-2x**, **(*R*)-III-2y** and **(*R*)-III-3u** by comparison of the sign of the optical rotation with that of previously reported compounds. Our results indicate that the copper-catalyzed reaction proceeds with inversion of the configuration. We assumed the same stereochemical outcome for all the enantiomerically enriched compounds prepared.

3.6.7.1. (–)-(R)-But-1-yne-1,3-diyldibenzene, ***(R)*-III-2b**.[96]

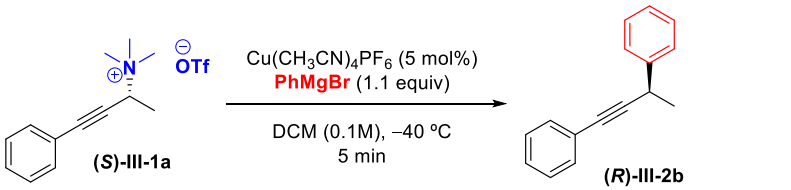
Previously reported



50%
e.r. = 95:5
$[\alpha]^{20}_{D}$ = +12.7(c 0.70, CH_2Cl_2).

Chem. Eur. J. **2012**, *18*, 9775-9779.

This work

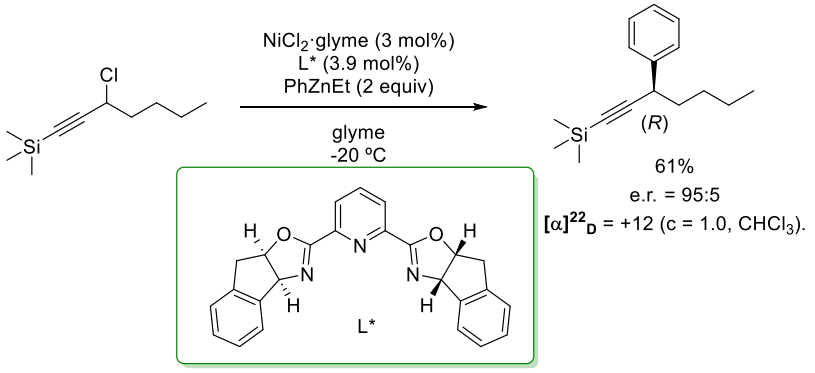


(*S*)-III-1a

(*R*)-III-2b
95%
e.r. = 98:2
$[\alpha]^{20}_{D}$= -16.3 (c = 1.0, $CHCl_3$).

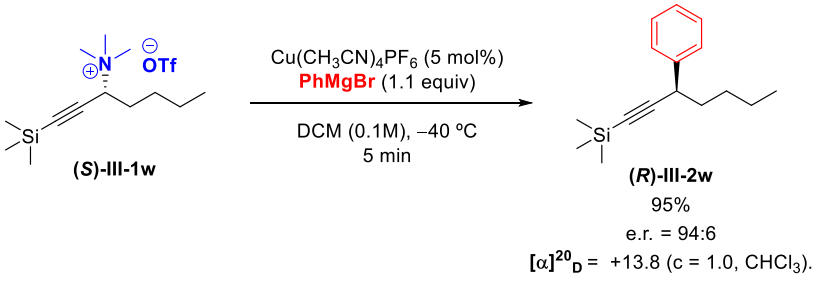
3.6.7.2. (+)-(R)-Trimethyl(3-phenylhept-1-yn-1-yl)silane, ***(R)*****-III-2w.**[51]

Previously reported



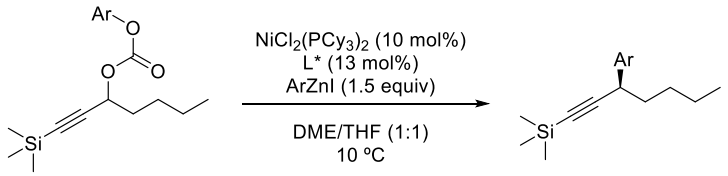
J. Am. Chem. Soc. **2008**, *130*, 12645-12647.

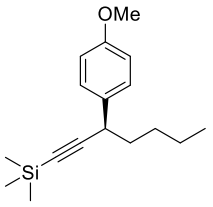
This work



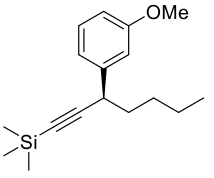
*3.6.7.3. (+)-(R)-(3-(4-Methoxyphenyl)hept-1-yn-1-yl)trimethylsilane, **(R)-III- 2x** and (+)-(R)-[3-(3-Methoxyphenyl)hept-1-yn-1-yl]trimethylsilane, **(R)-III-2y**.*[52]

Previously reported





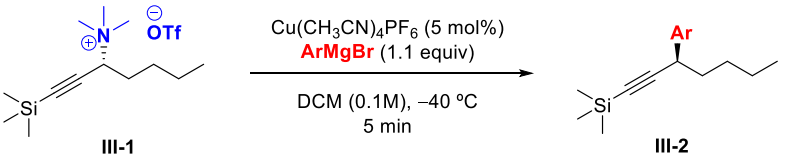
75%
e.r. = 94:6
$[\alpha]^{22}_{D}$ = +4.7 (c = 0.48, $CHCl_3$).



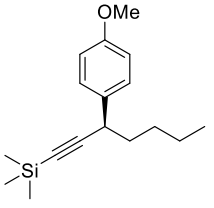
73%
e.r. = 95:5
$[\alpha]^{23}_{D}$ = +16 (c = 0.67, $CHCl_3$).

J. Am. Chem.Soc. **2012**, *134*, 2966-2969.

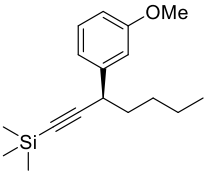
This work



III-1 **III-2**



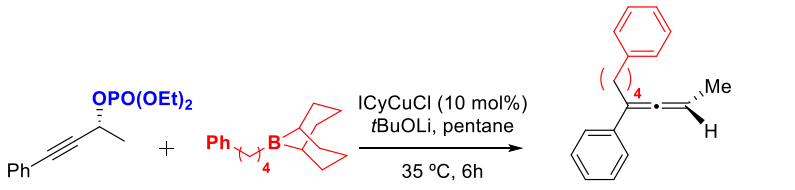
(*R*)-III-2x
82%
e.r. = 93:7
$[\alpha]^{22}_{D}$ = +7.9 (c = 1.0, $CHCl_3$).



(*R*)-III-2y
87%
e.r. = 94:6
$[\alpha]^{23}_{D}$ = +8.2 (c = 1.0, $CHCl_3$).

3.6.7.4. *(–)-(R)-Octa-5,6-diene-1,5-diyldibenzene,* ***(R)-III-3u***.[99]

Previously reported

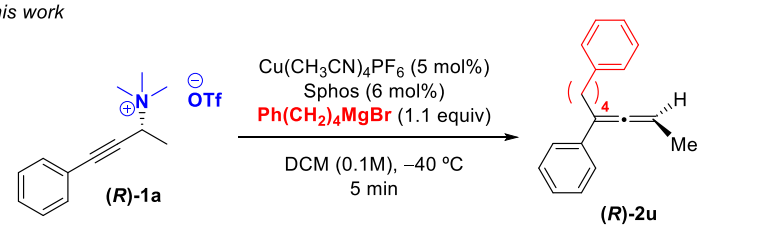


99% ee

(*S*)-3
93%
er 98:2
$[\alpha]^{20}_D$ = +90.6(c 1.4, CH_2Cl_2).

Org. Lett. **2012**, *14*, 362.

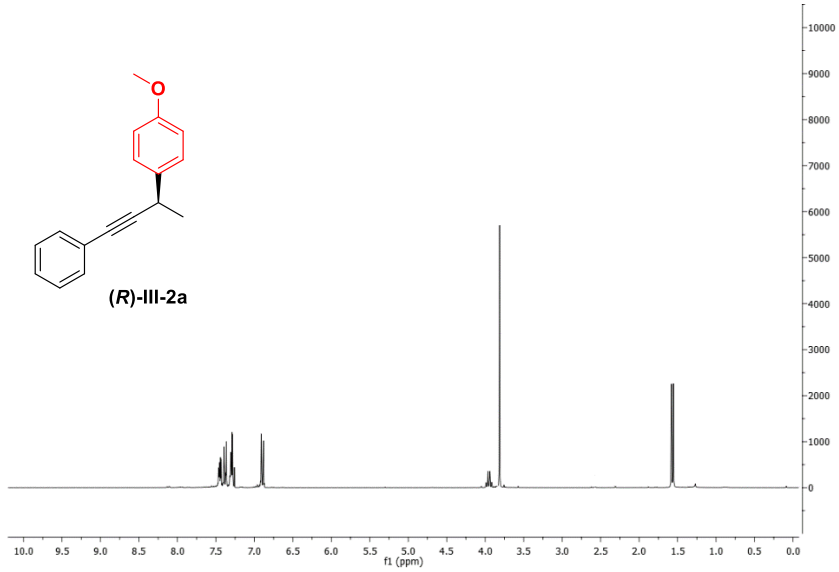
This work

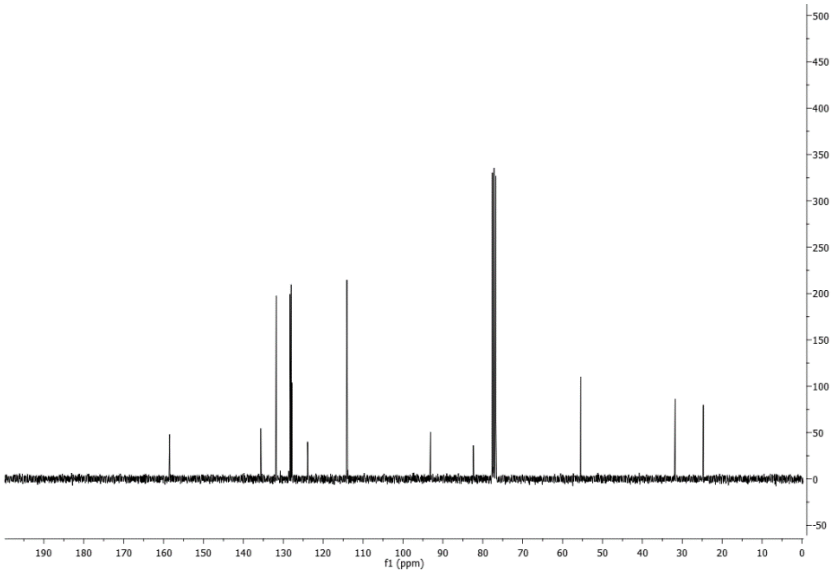


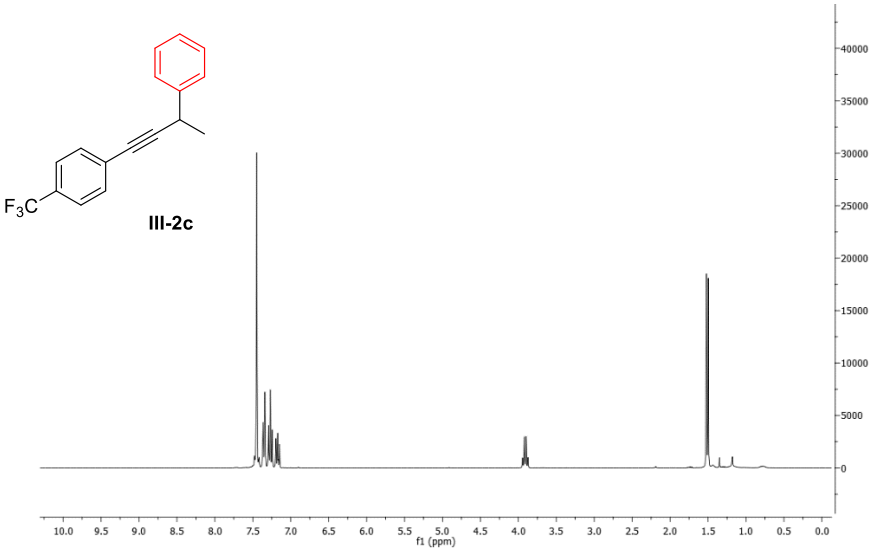
(*R*)-1a

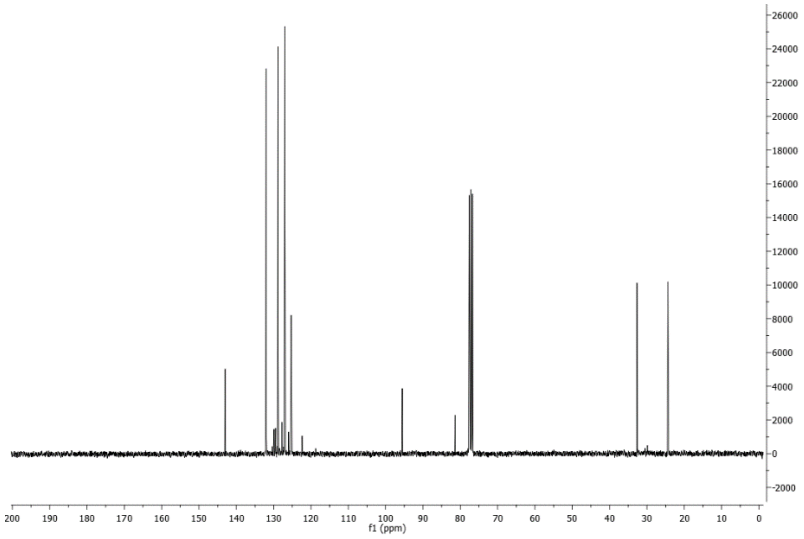
(*R*)-2u
90%
er 98:2
$[\alpha]^{20}_D$= -54.0 (c = 1.0, $CHCl_3$).

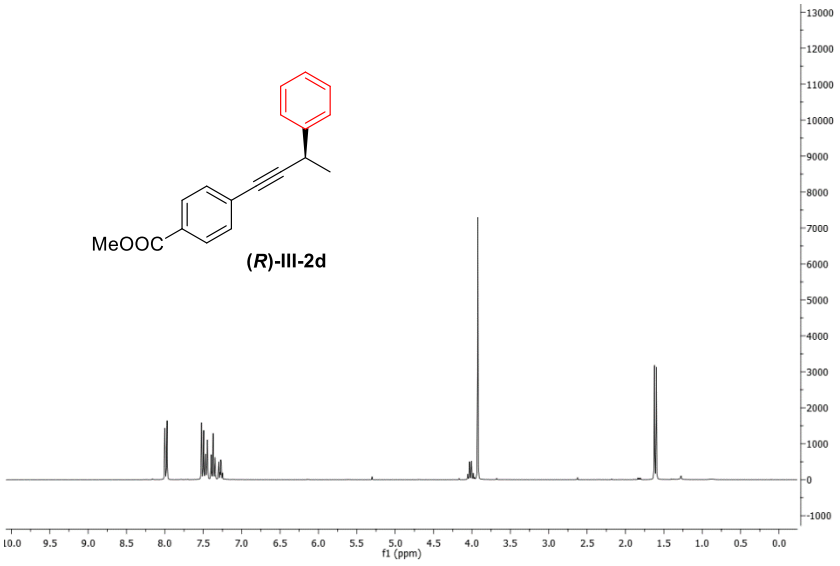
3.7. NMR Spectra.

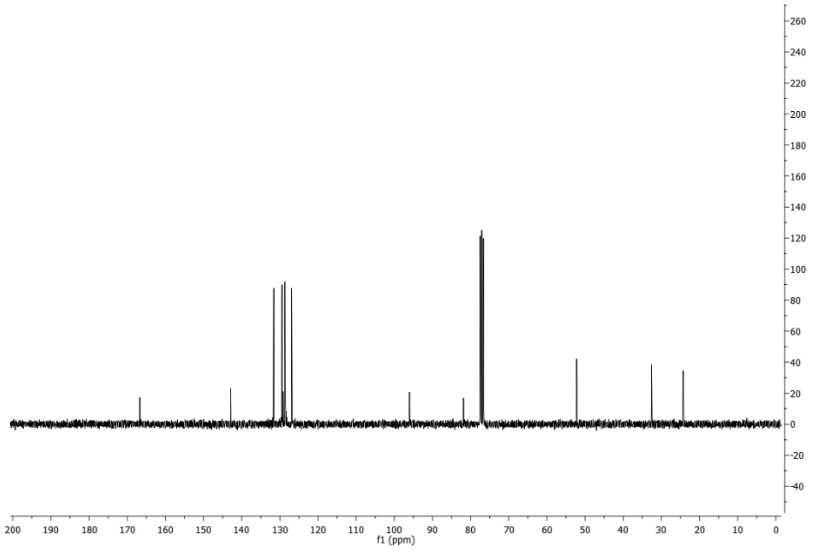


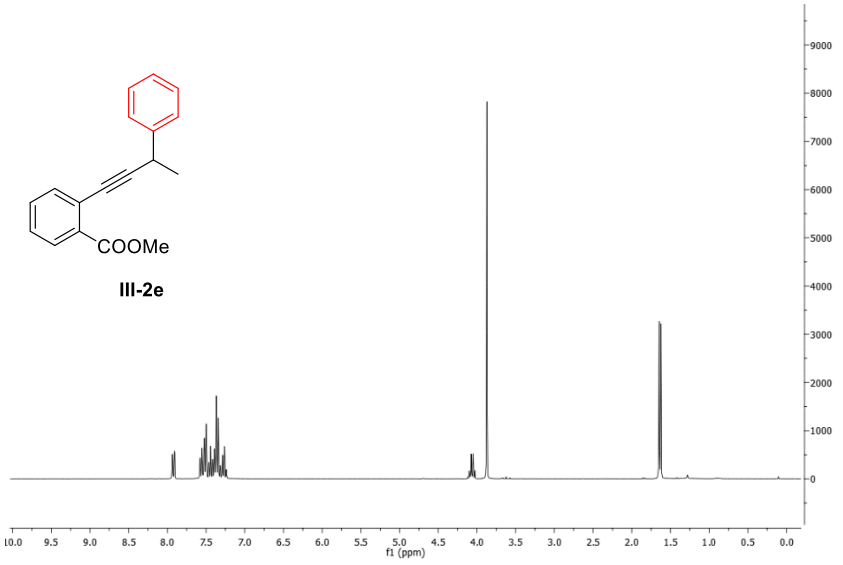



F3C
III-2c
40000
35000
30000
25000
20000
15000
10000
5000
0
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

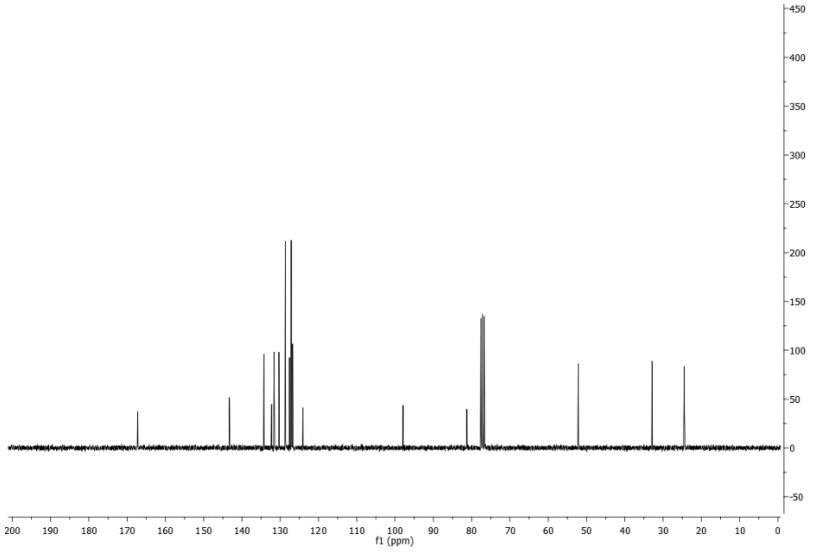

26000
24000
22000
20000
18000
16000
14000
12000
10000
8000
6000
4000
2000
0
-2000
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

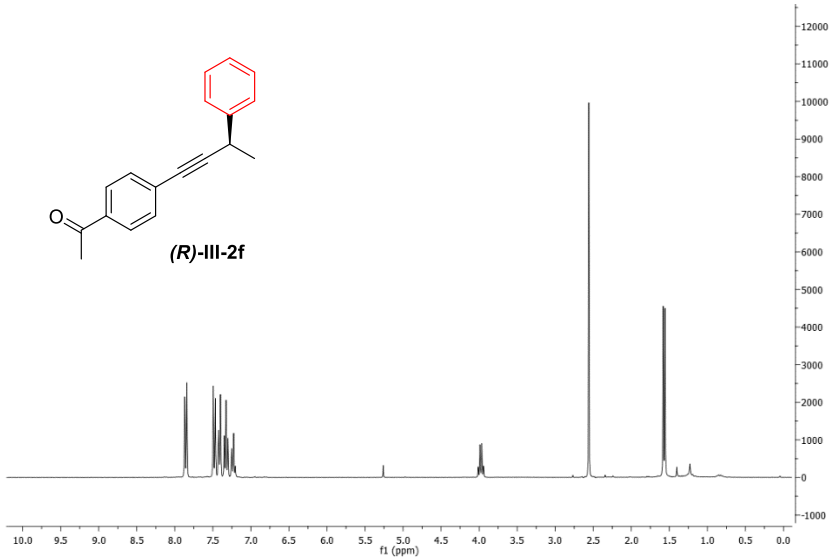

MeOOC
(R)-III-2d
f1 (ppm)

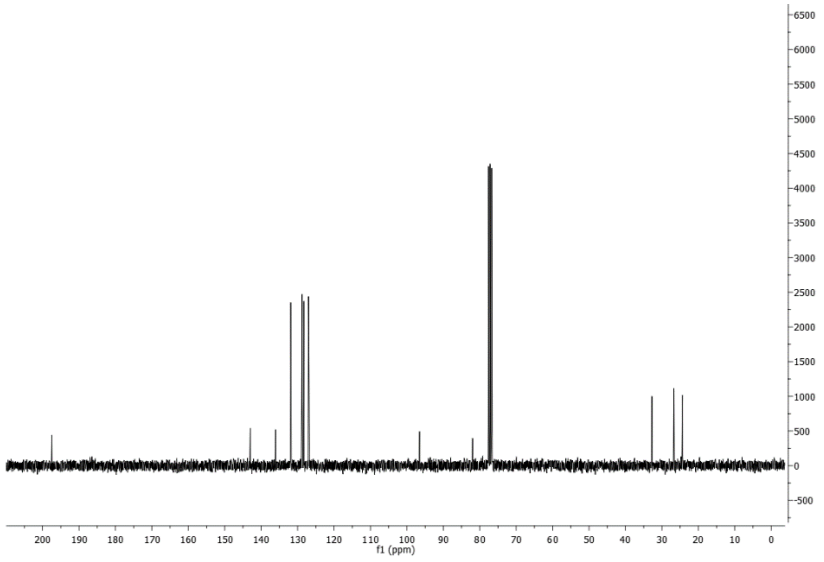

f1 (ppm)

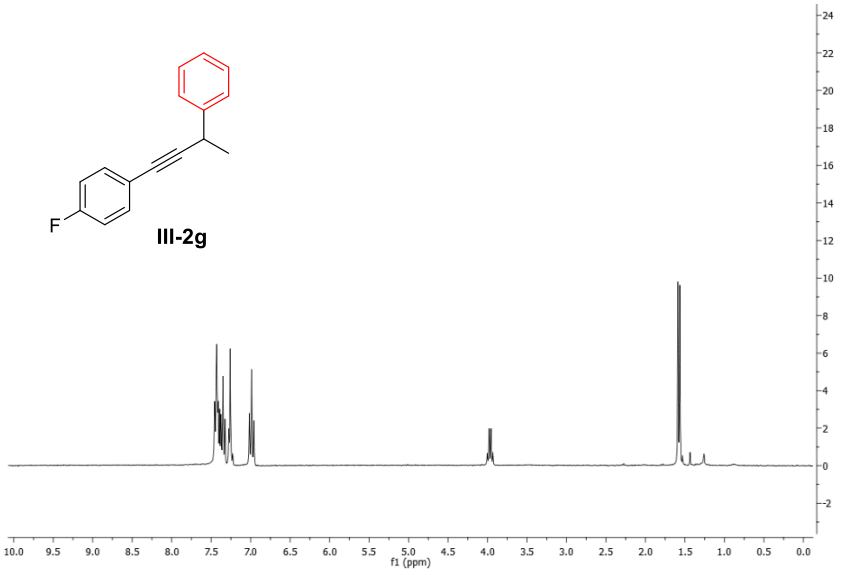


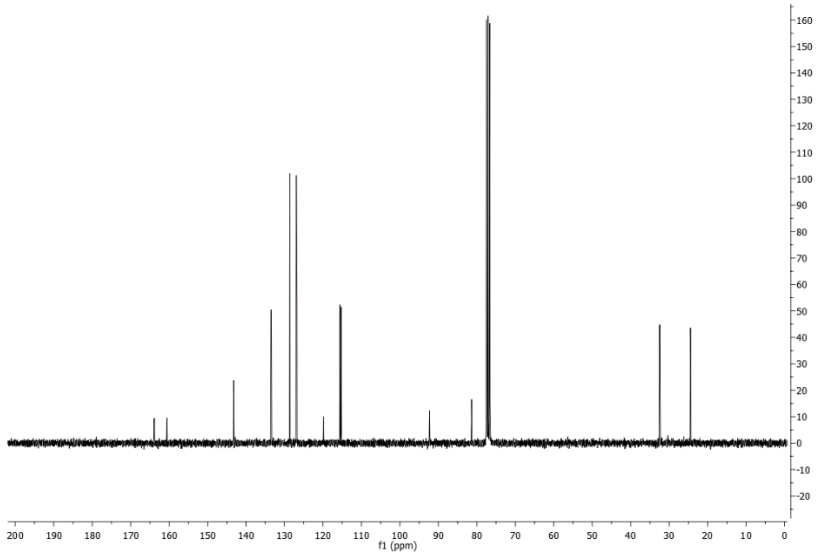
III-2e

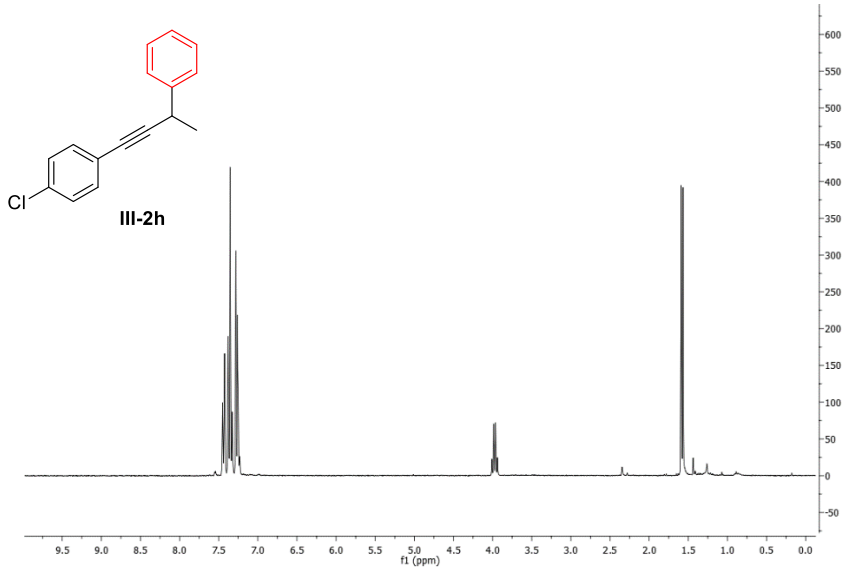


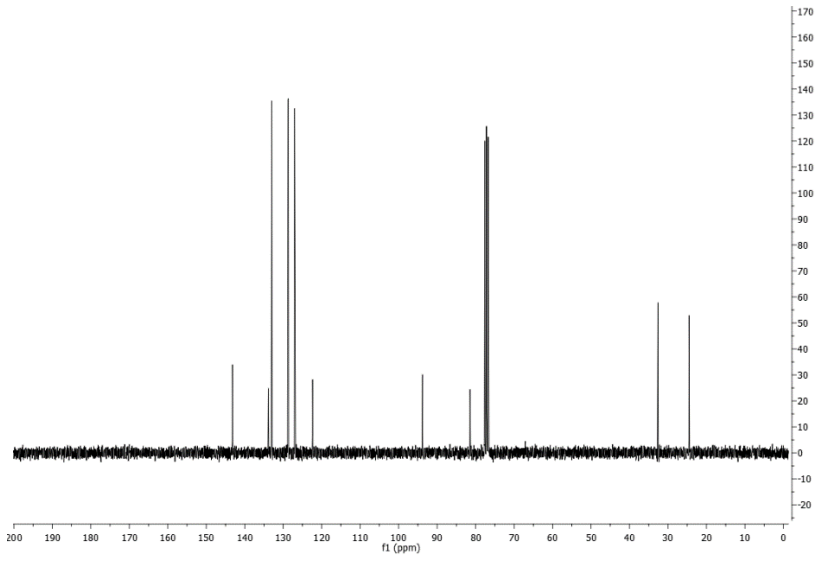

O
(R)-III-2f
f1 (ppm)

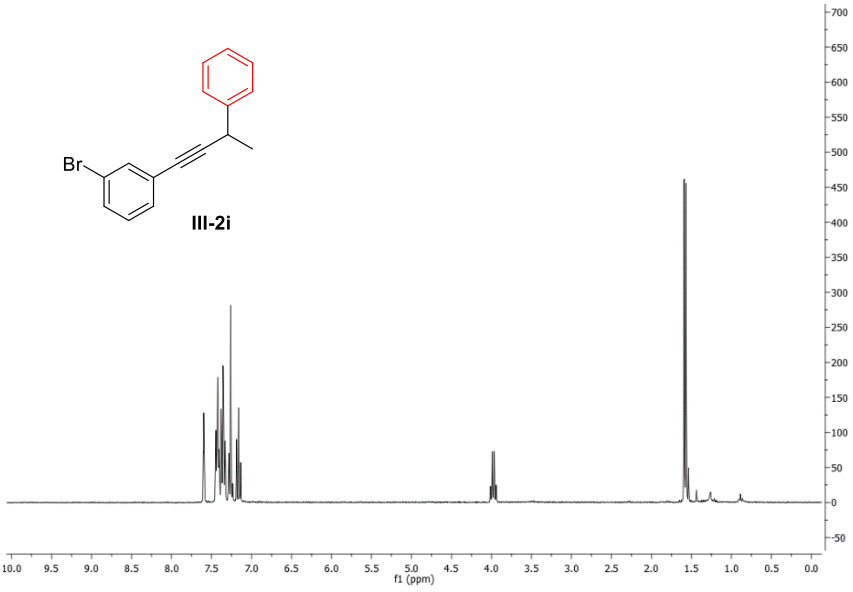

f1 (ppm)

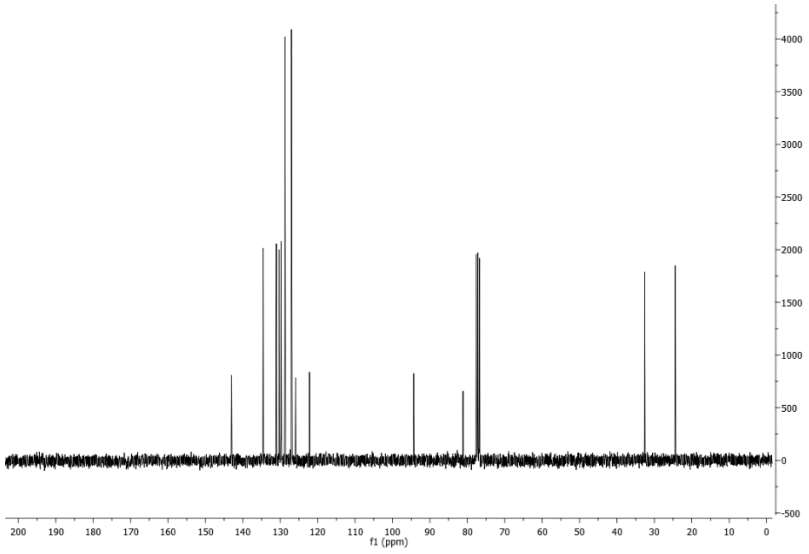

F
III-2g
f1 (ppm)

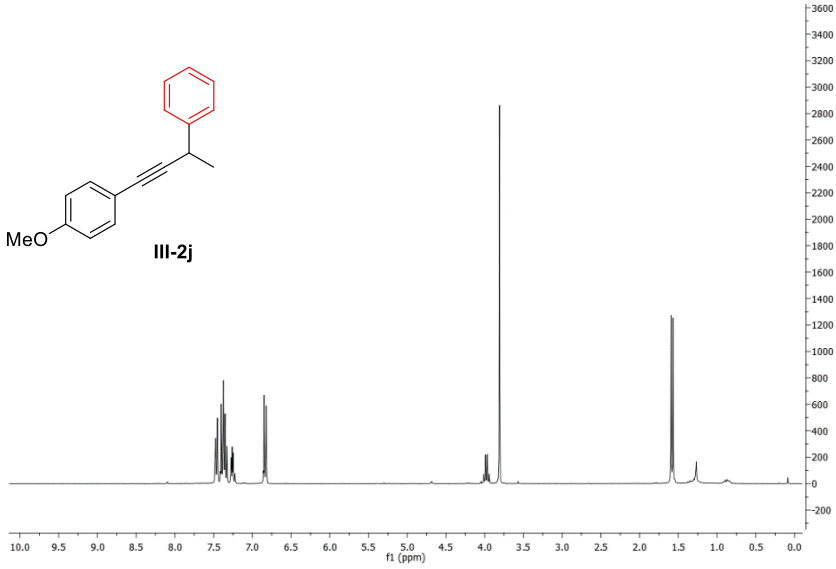

f1 (ppm)

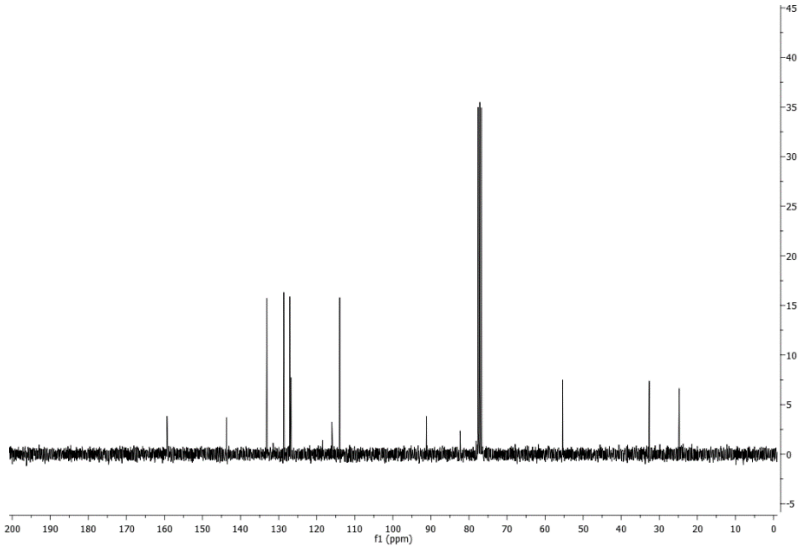

Cl
III-2h
f1 (ppm)

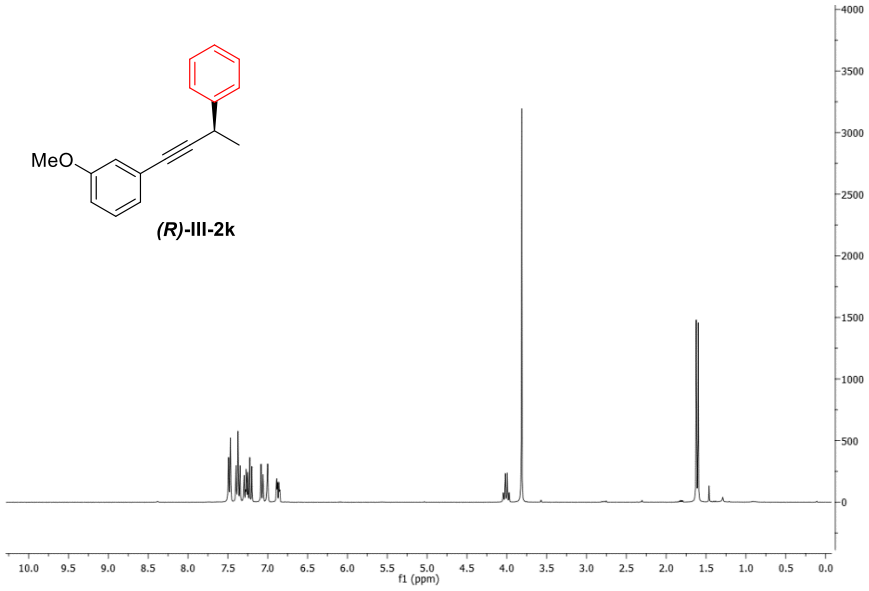

f1 (ppm)


Br
III-2i
f1 (ppm)

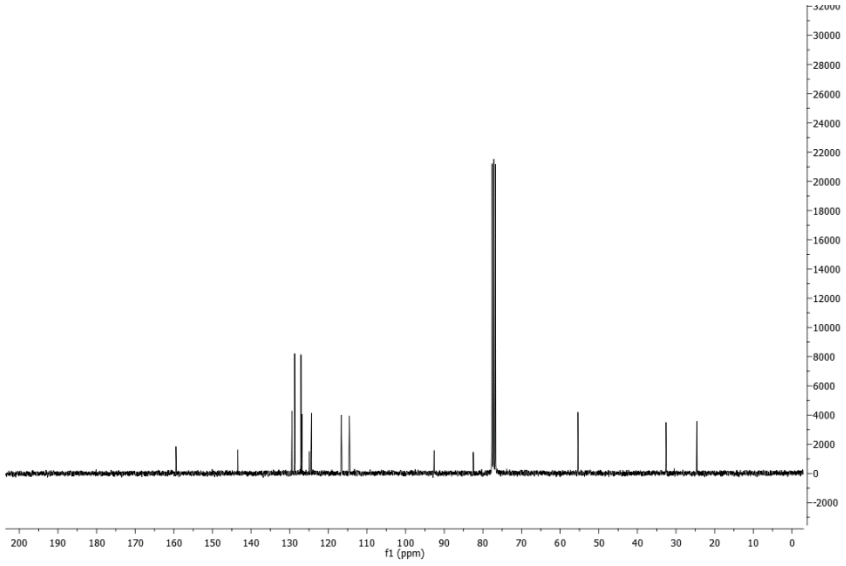

f1 (ppm)

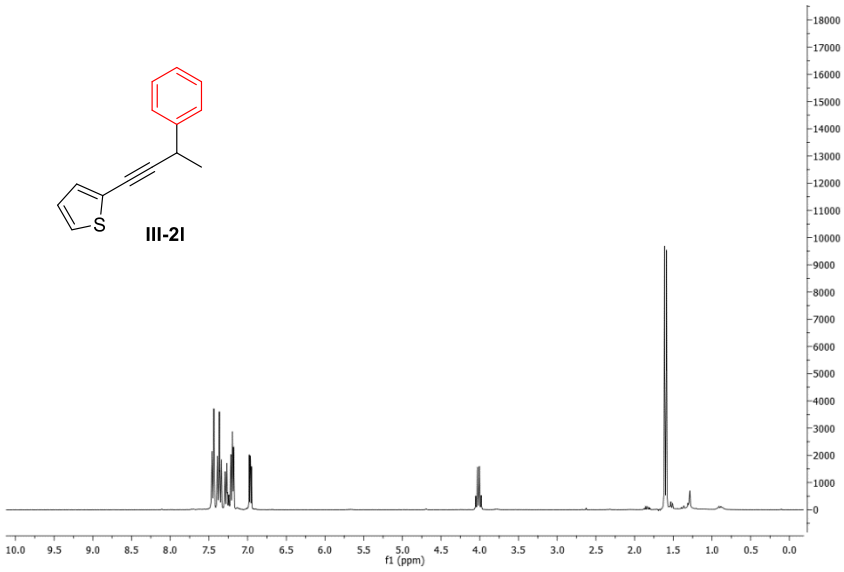

MeO
III-2j
f1 (ppm)

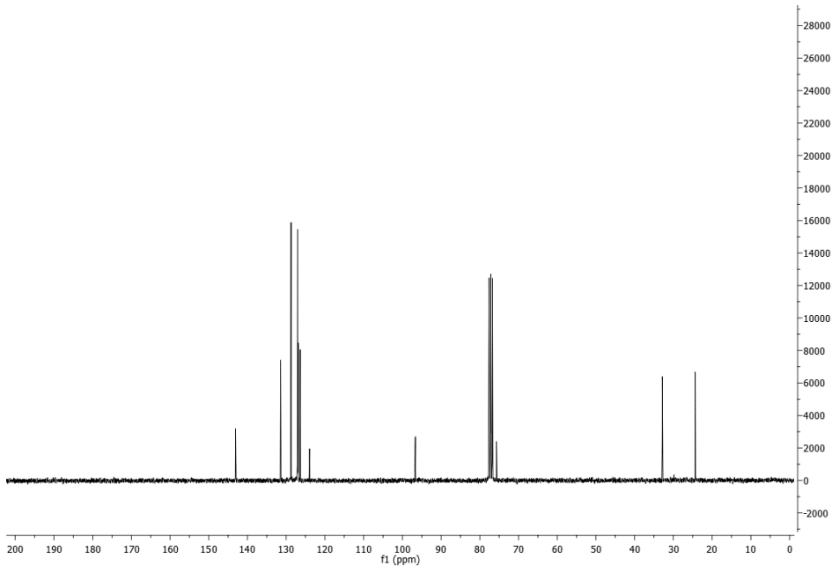

f1 (ppm)

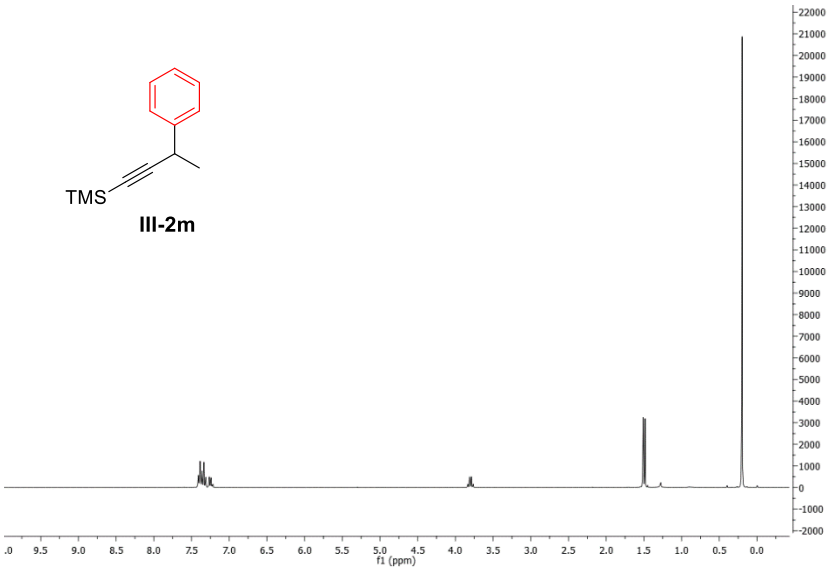


***(R)*-III-2k**

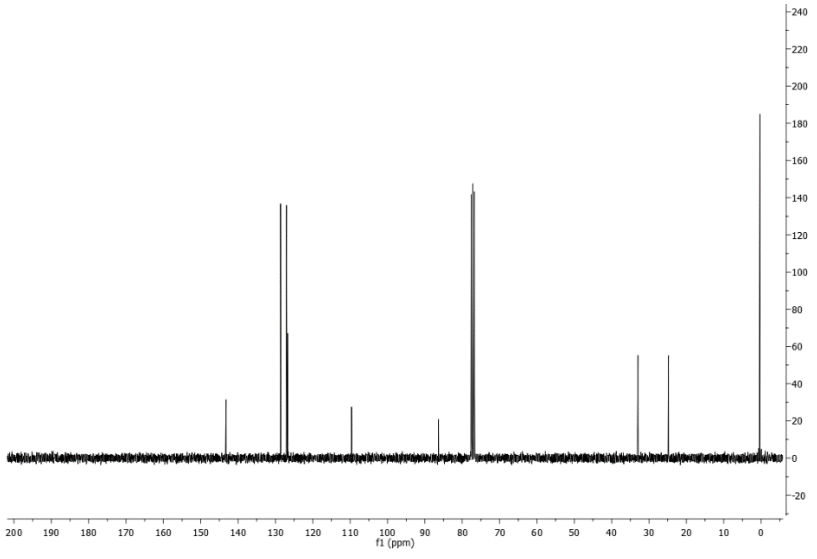


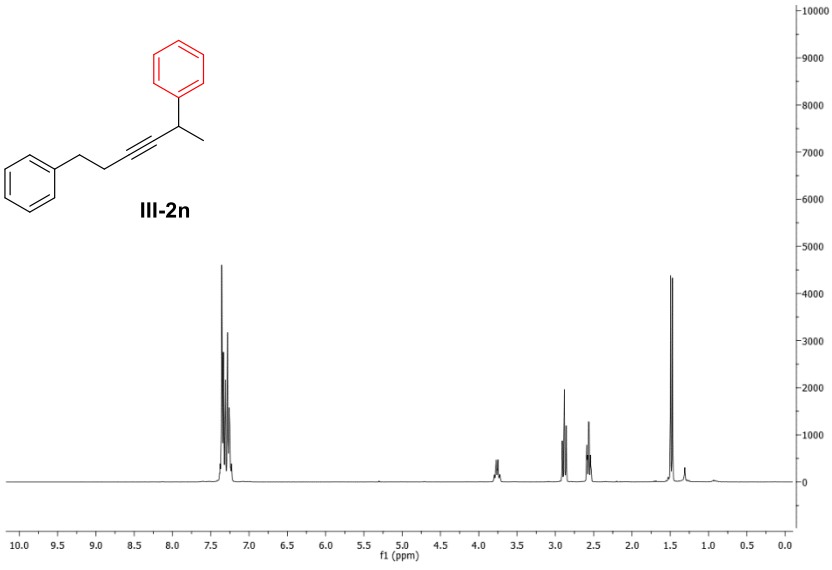

S
III-2l
f1 (ppm)

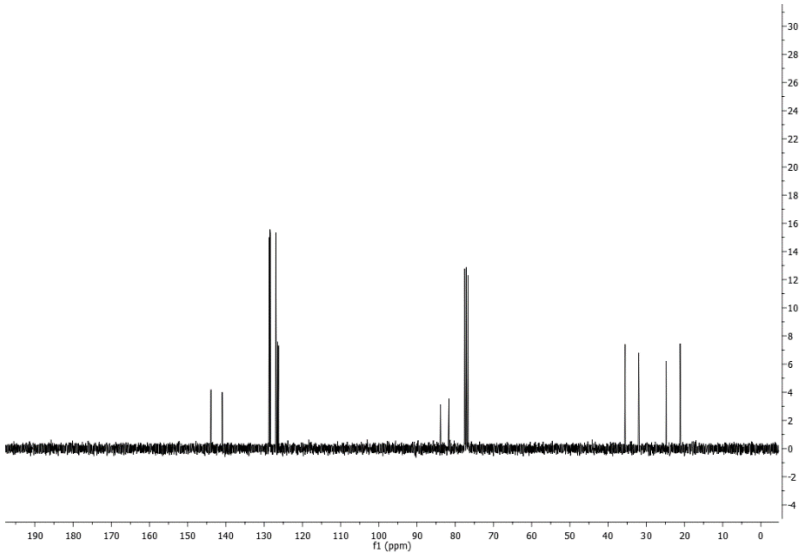

f1 (ppm)

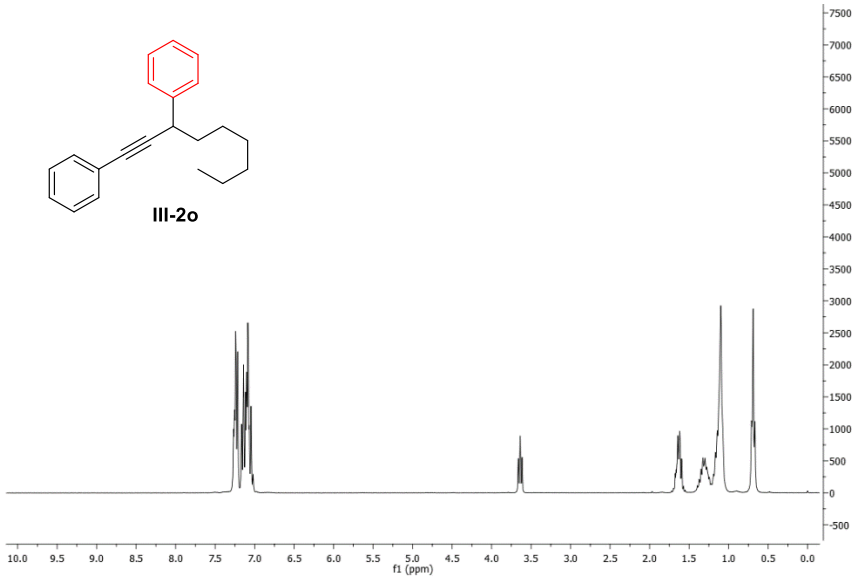


III-2m




III-2n
f1 (ppm)


f1 (ppm)


III-2o
7500
7000
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
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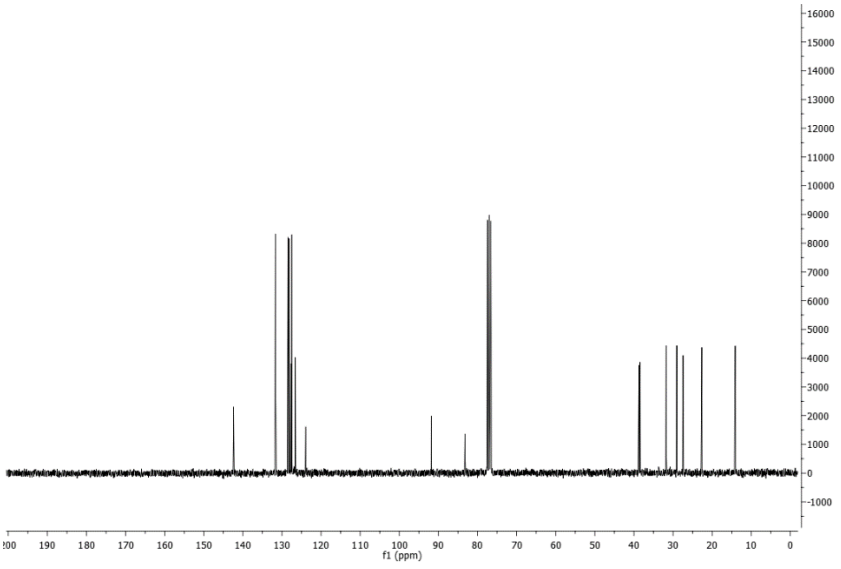
-500
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


16000
15000
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11000
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9000
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6000
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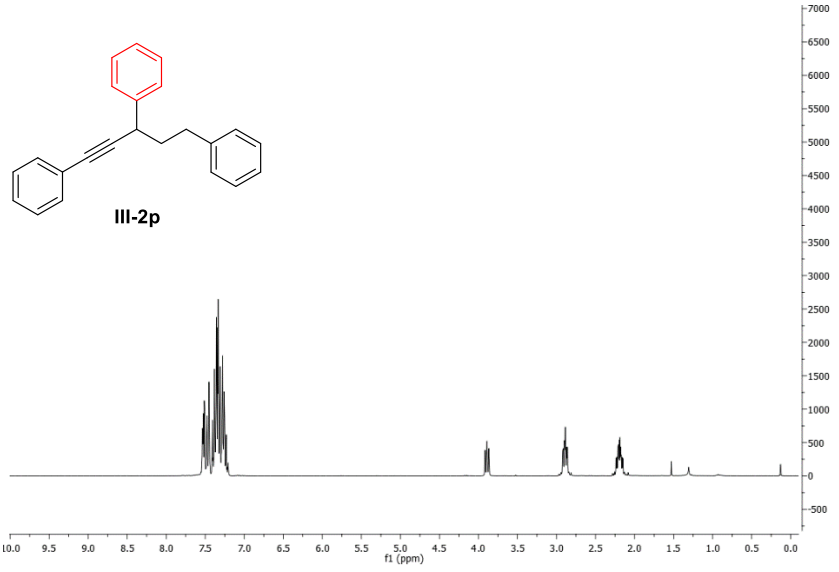
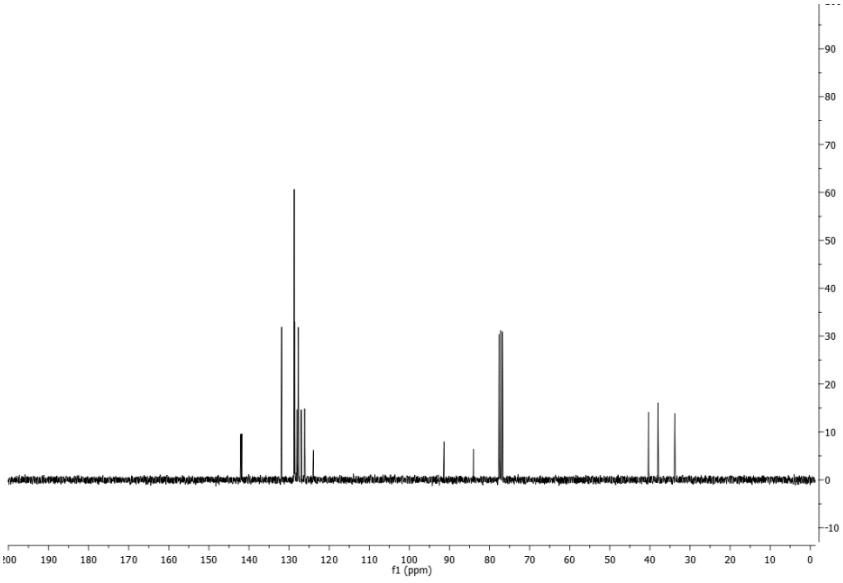
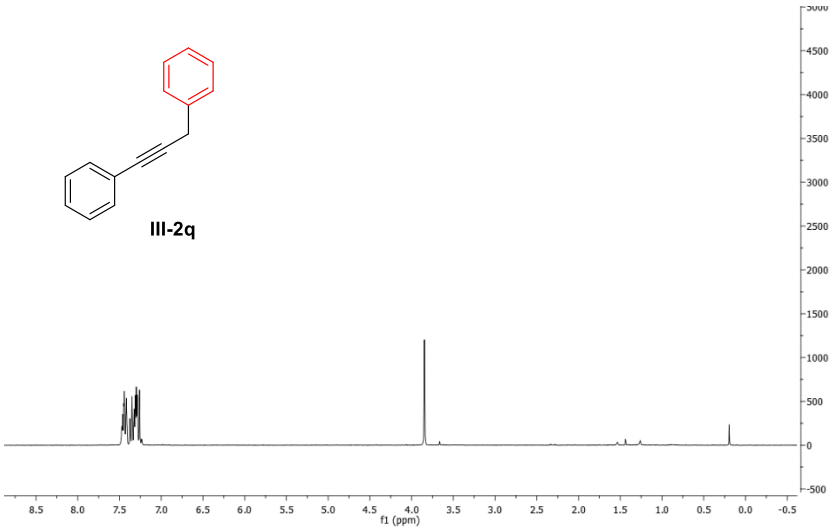
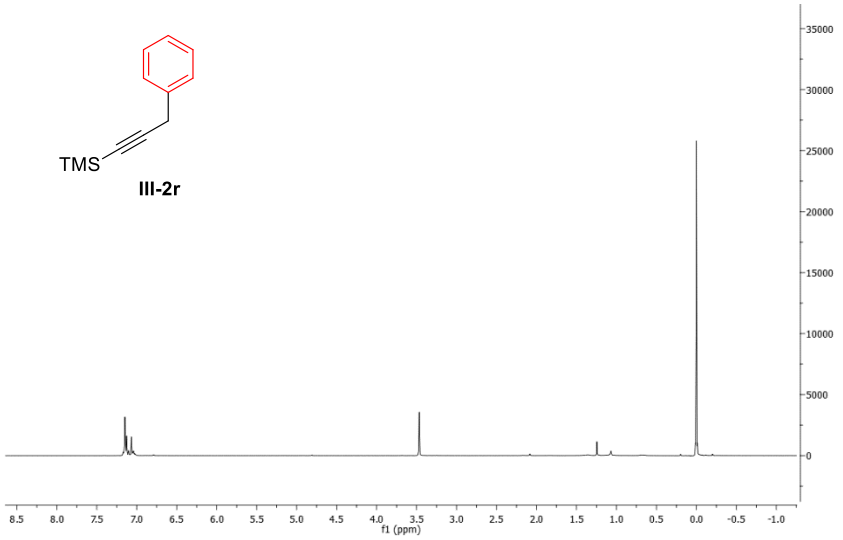
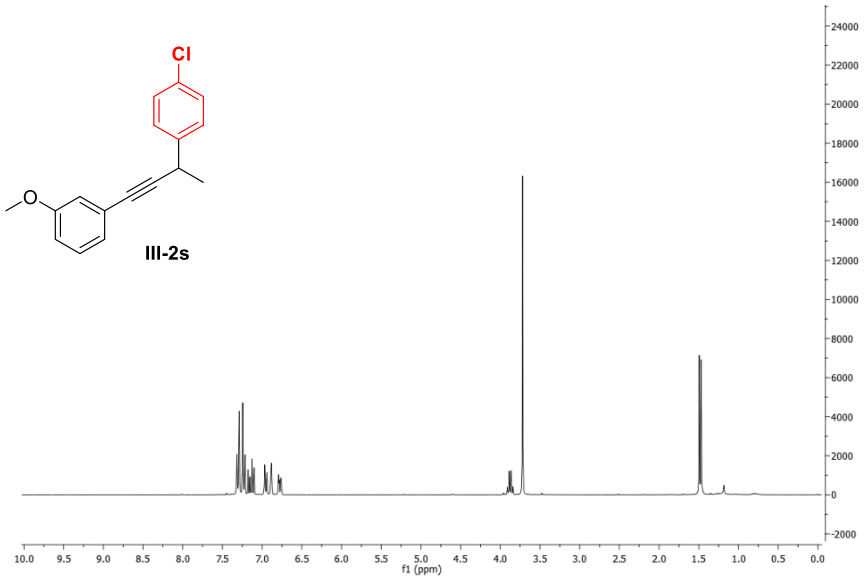
4000
3000
2000
1000
0
-1000
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

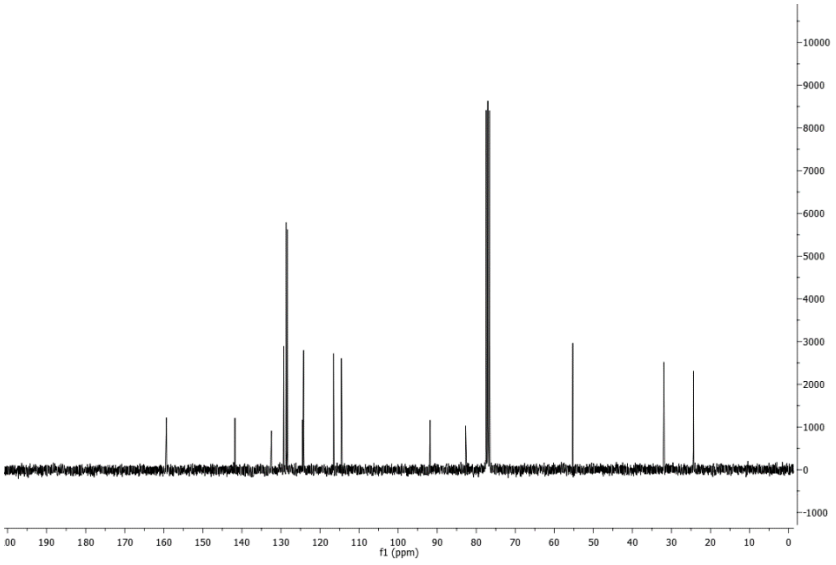

III-2p
f1 (ppm)

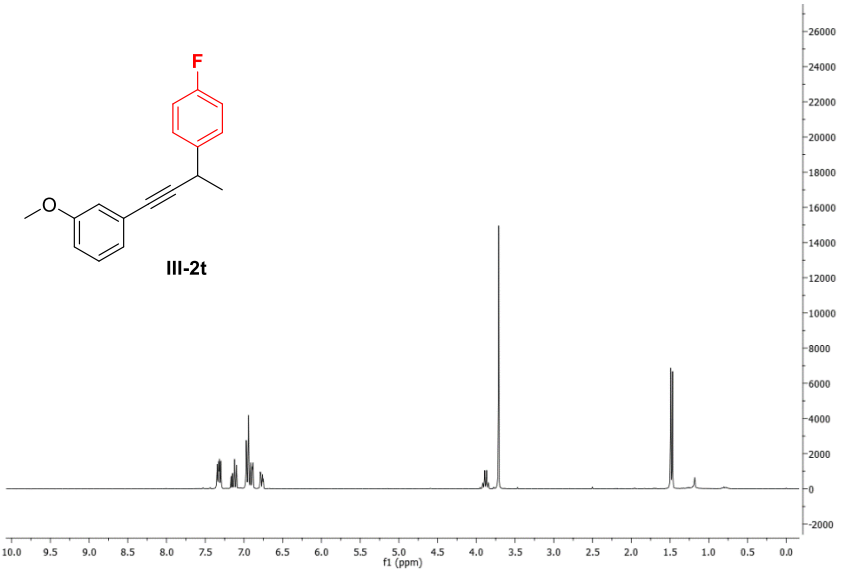

f1 (ppm)

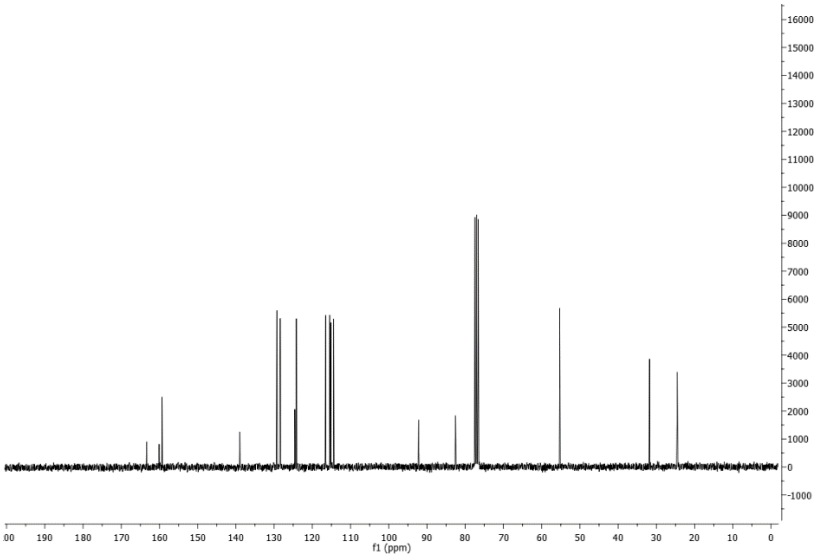

III-2q
f1 (ppm)

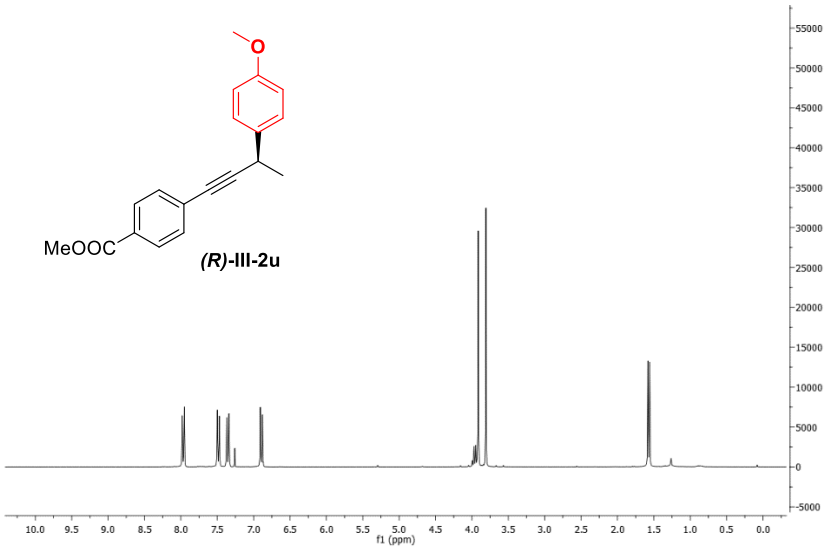

TMS
III-2r
f1 (ppm)


Cl
O
III-2s
f1 (ppm)

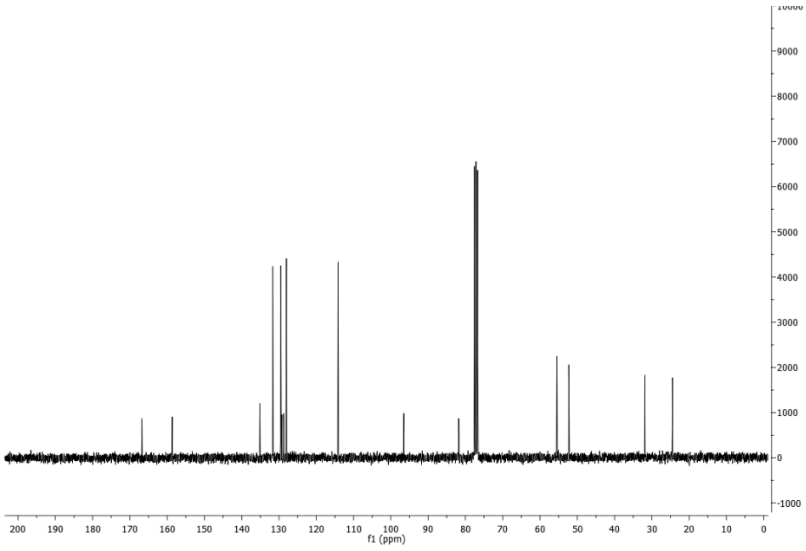

f1 (ppm)

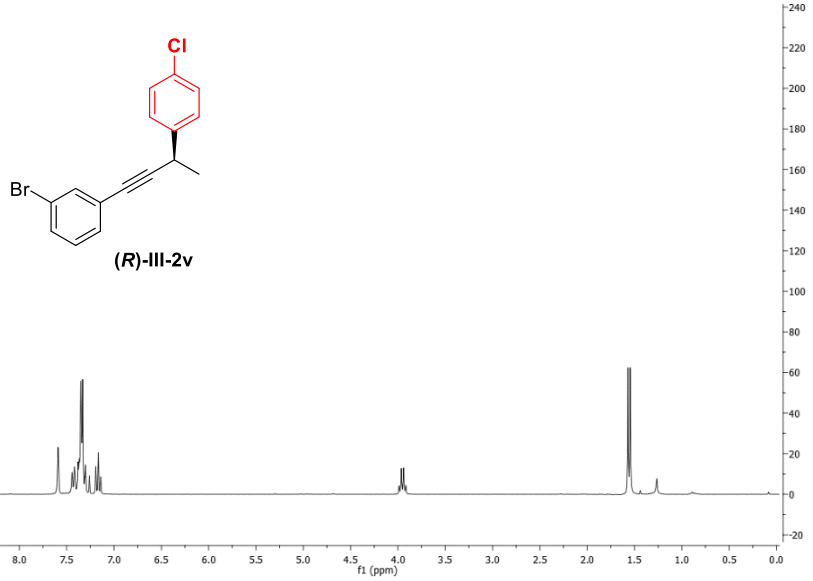

F
O
III-2t
f1 (ppm)

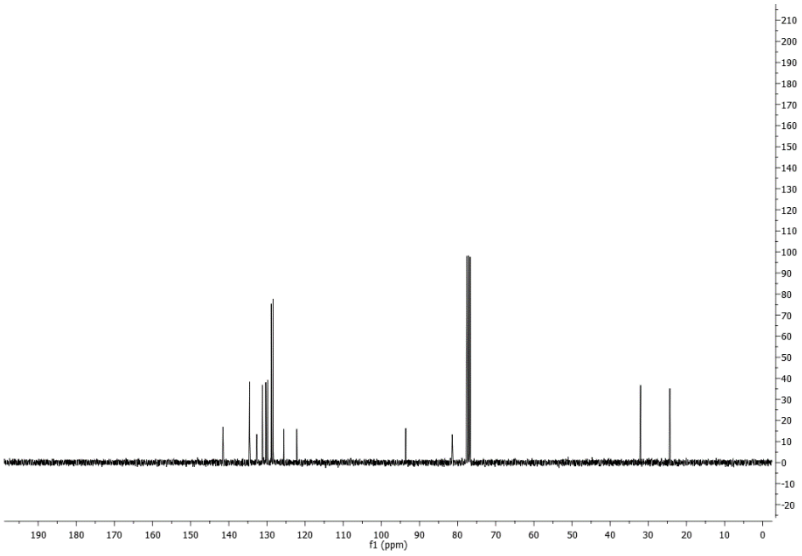

f1 (ppm)

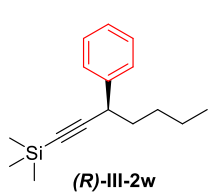


***(R)*-III-2u**

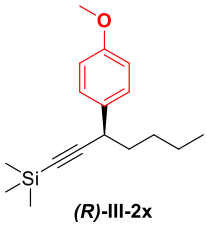



Cl
Br
(*R*)-III-2v
f1 (ppm)

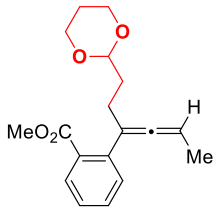

f1 (ppm)



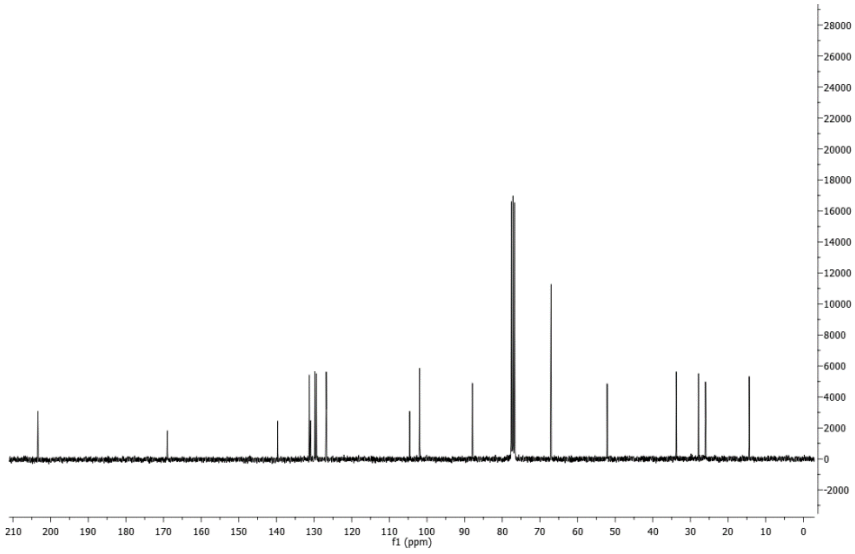
***(R)*-III-2w**

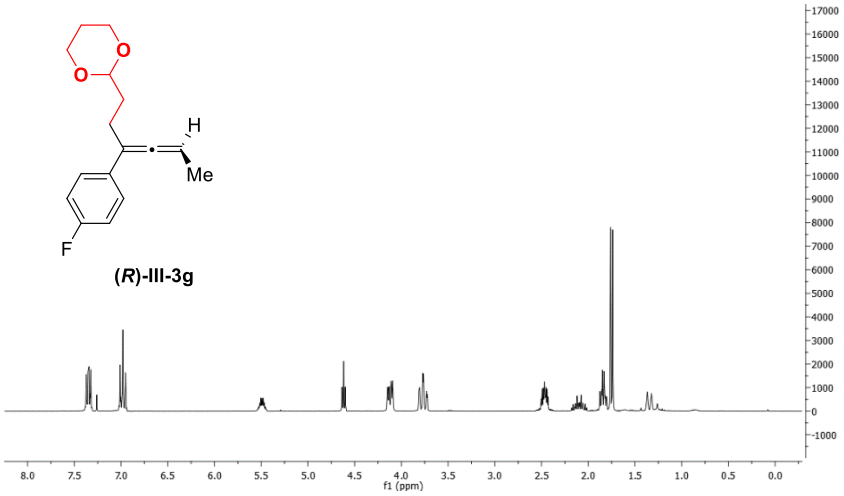


***(R)*-III-2x**

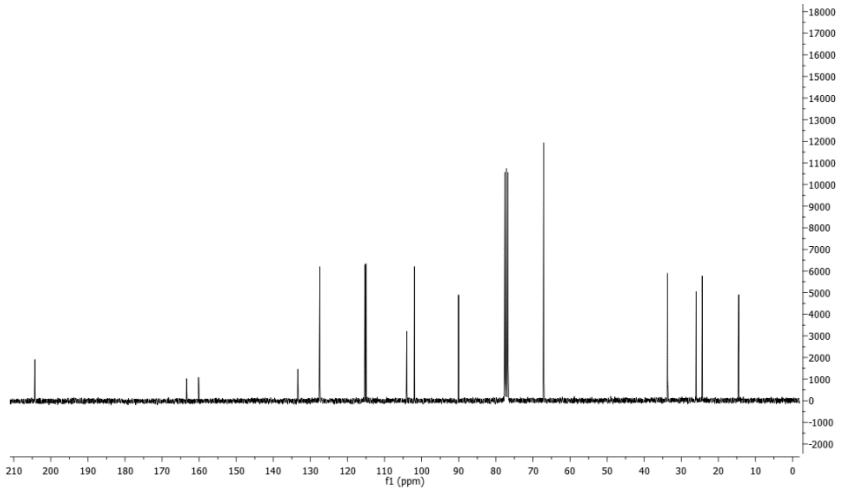


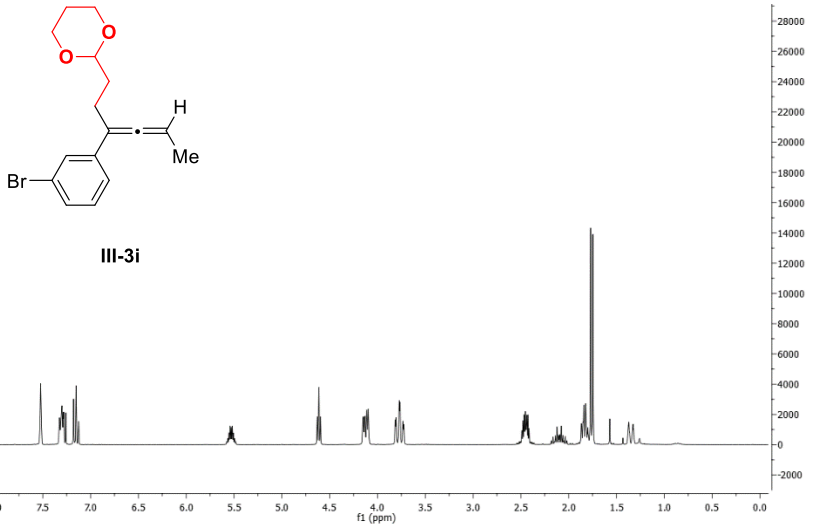
III-3e



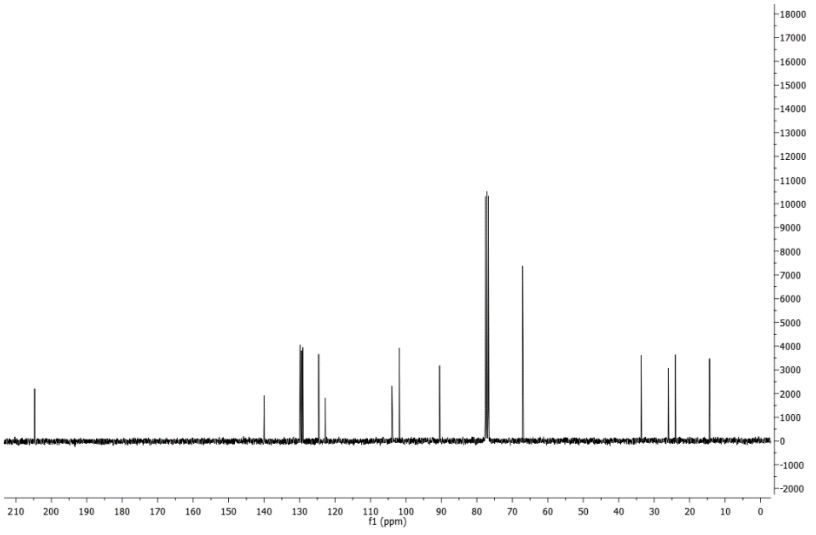


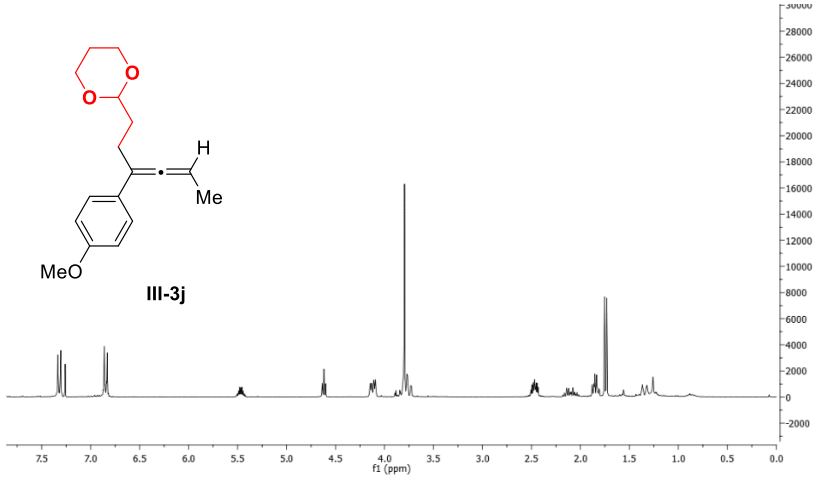
(*R*)-III-3g



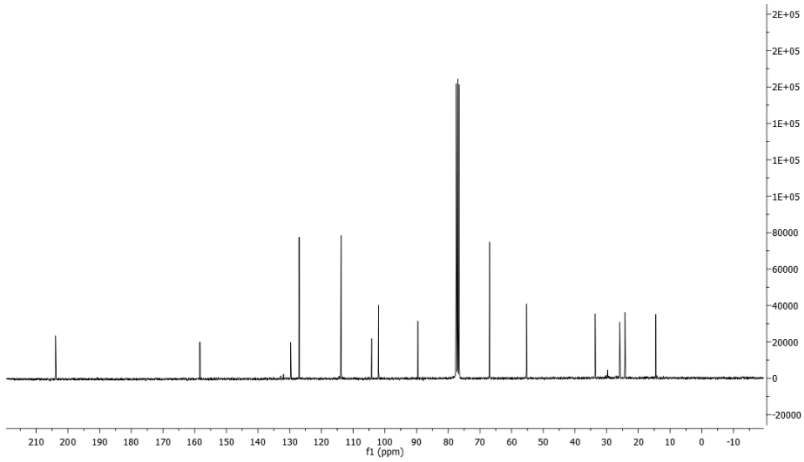


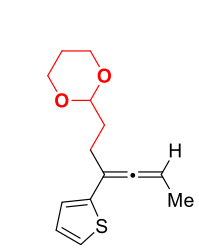
III-3i



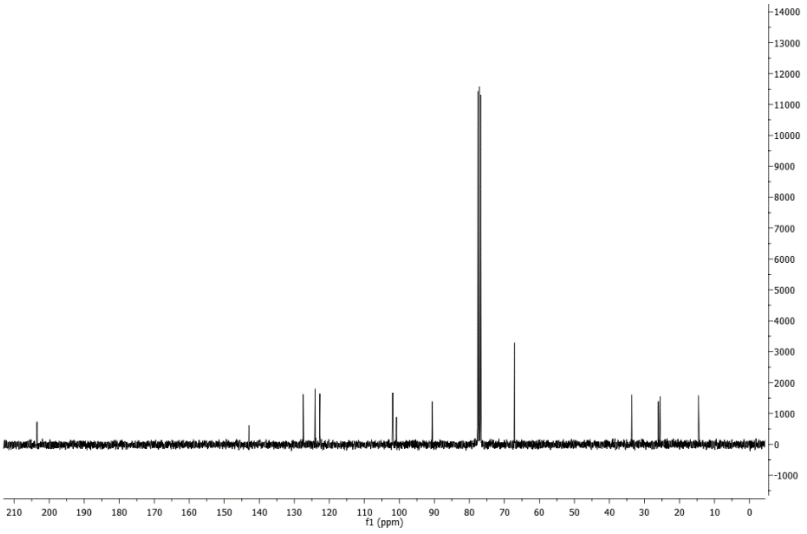


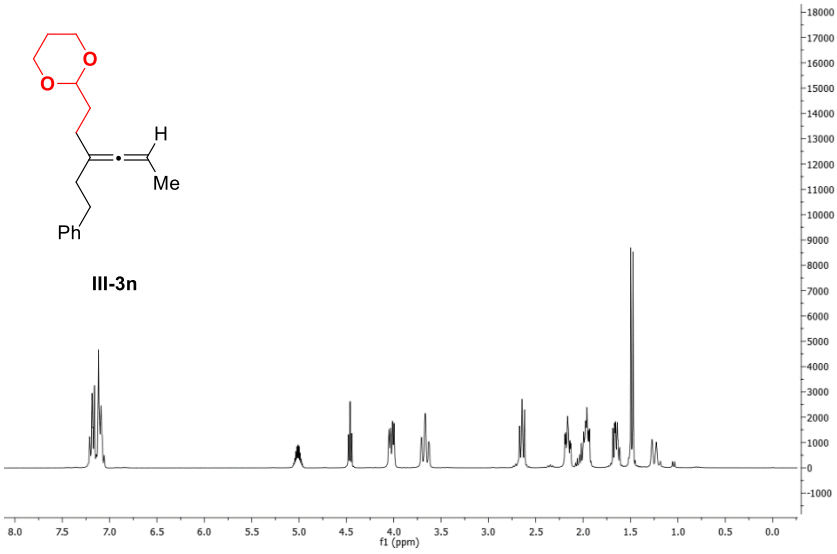
III-3j

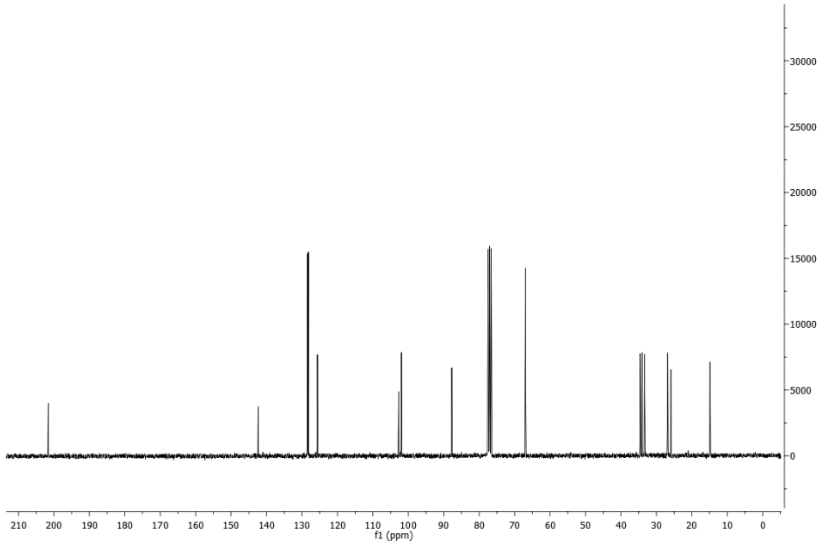


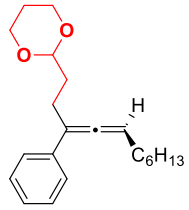


III-3l



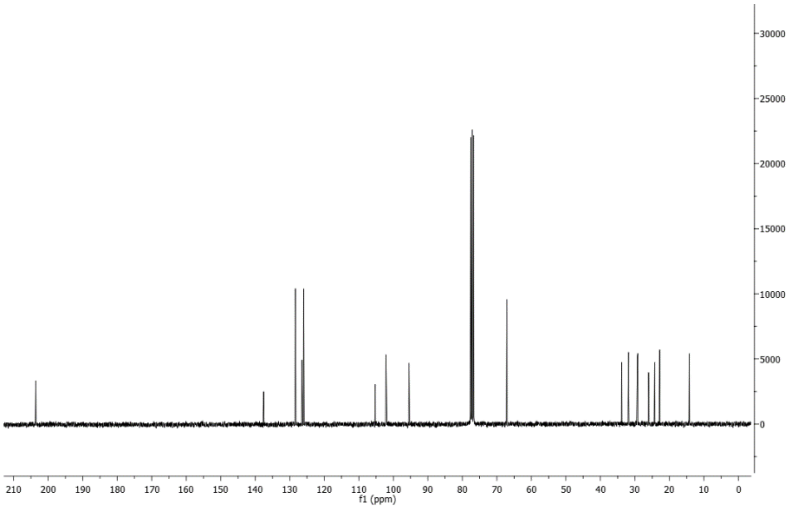

O
O
H
Me
Ph
III-3n
f1 (ppm)

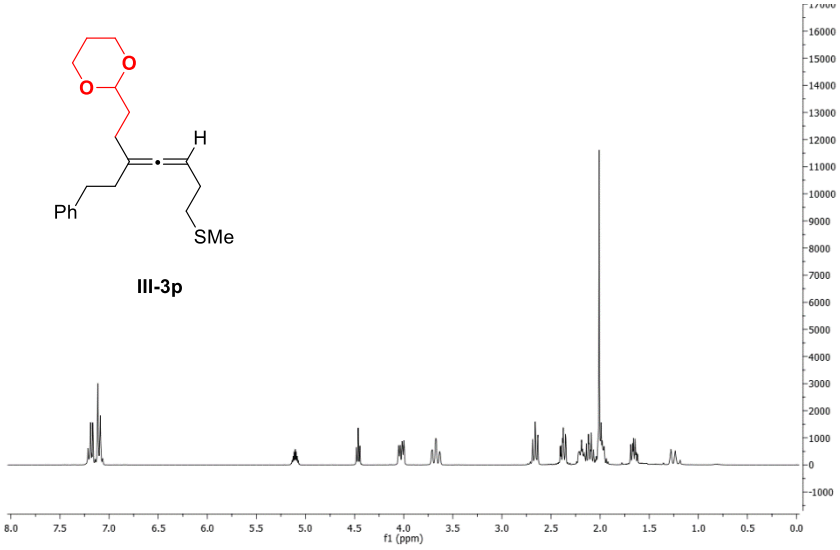

f1 (ppm)


O
O
H
C_6H_{13}

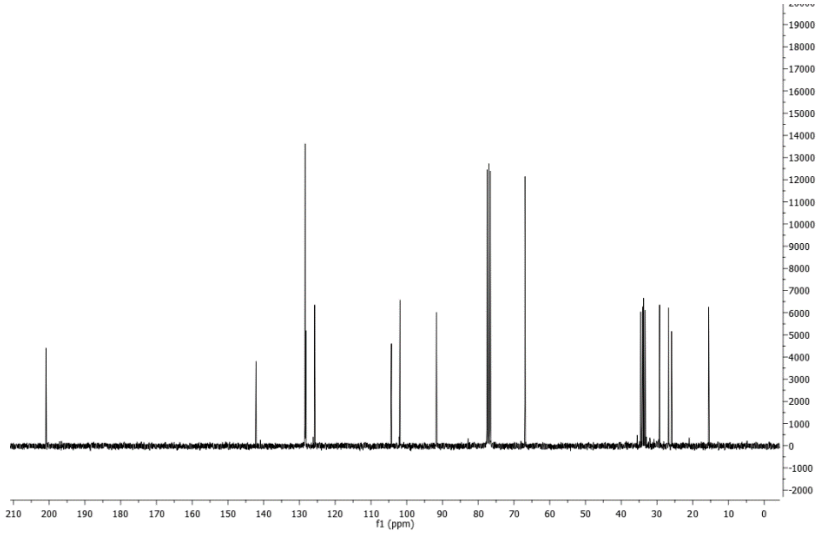
(*R*)-III-3o

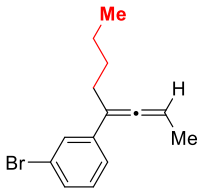
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


30000
25000
20000
15000
10000
5000
0
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)



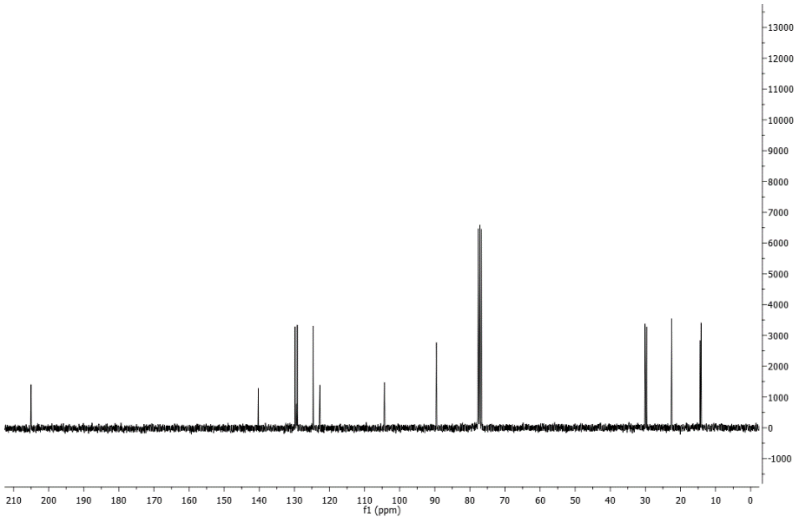
III-3p

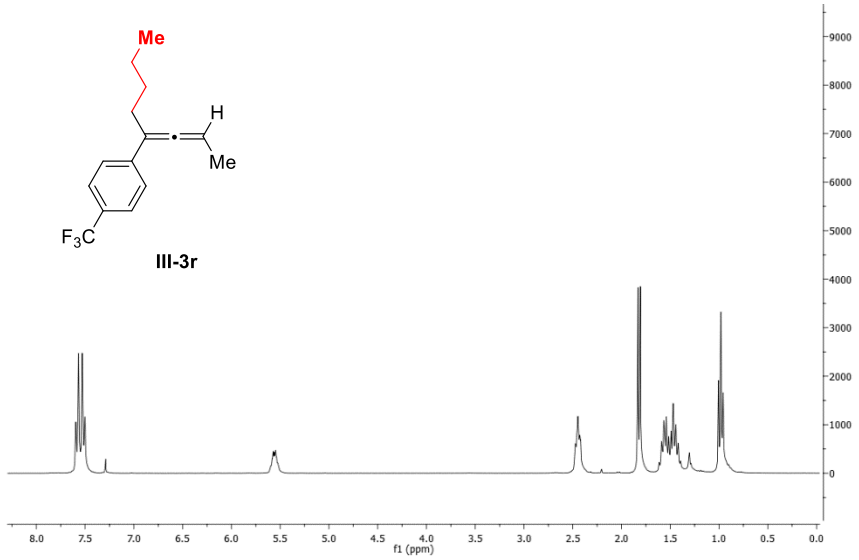



Me
H
Me
Br

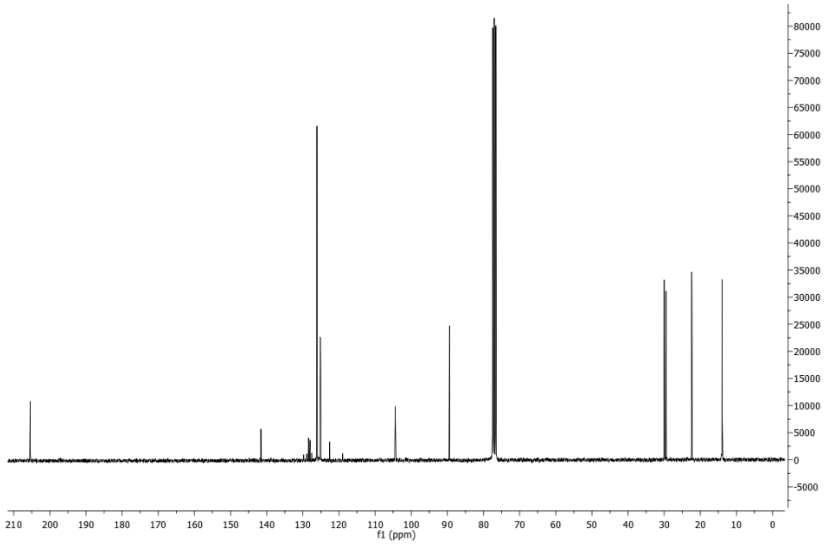
III-3q

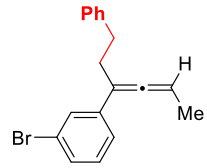
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

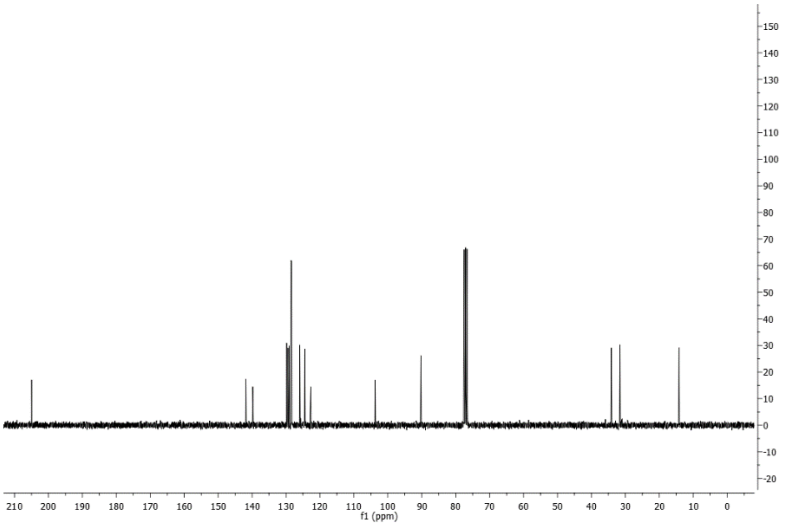


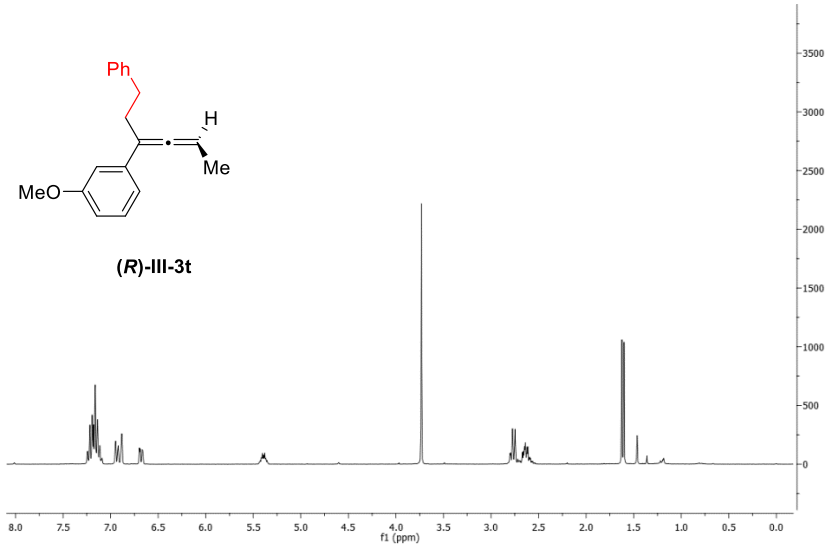
III-3r

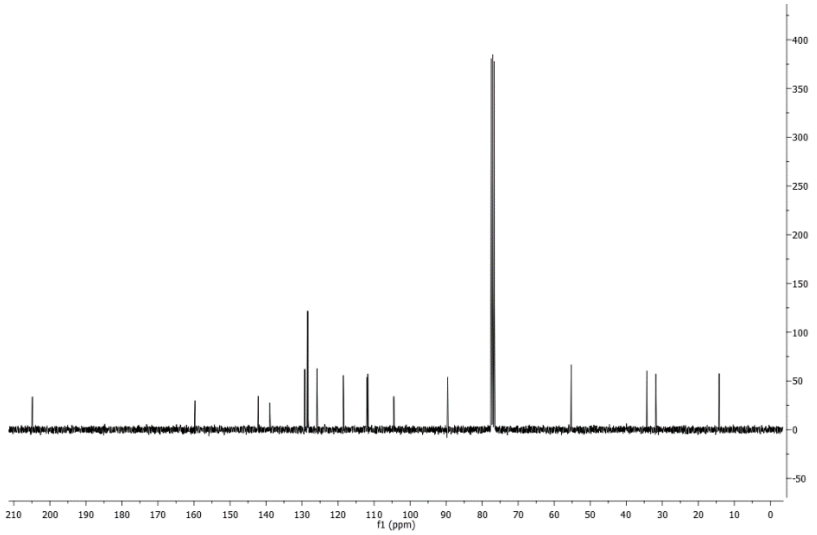


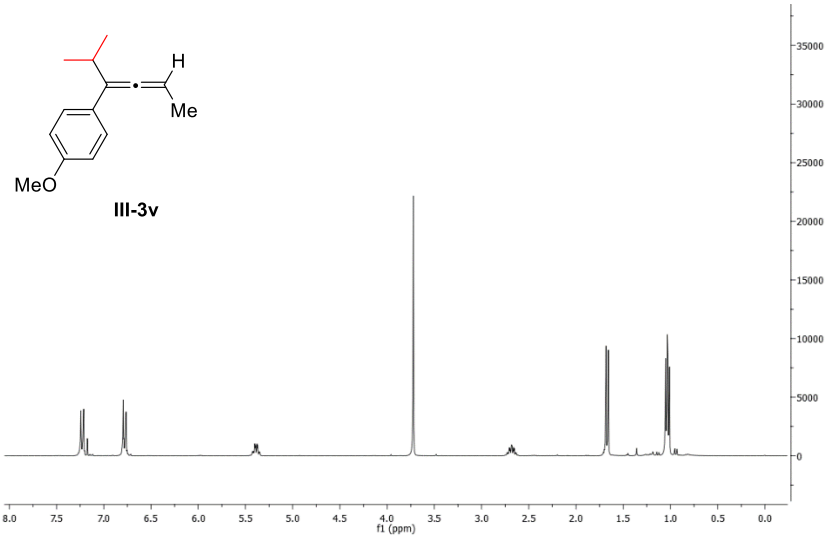


III-3s

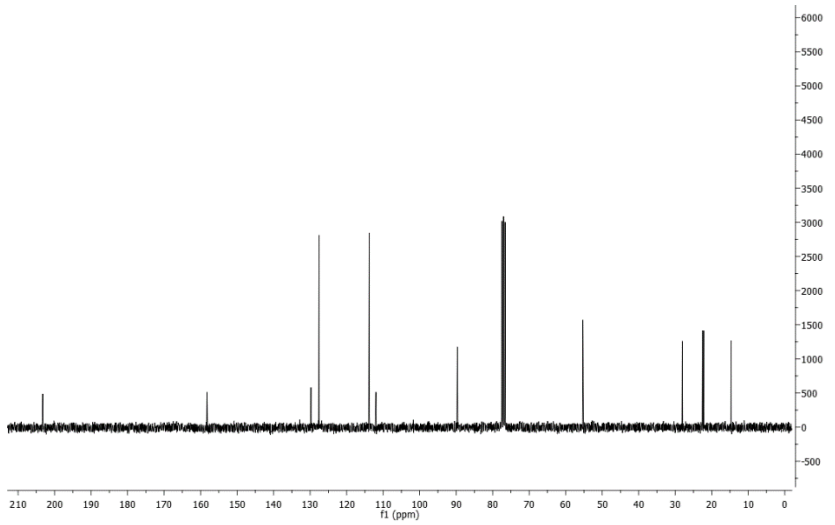


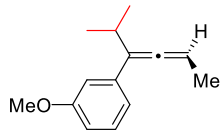

Ph
H
Me
MeO
(R)-III-3t
f1 (ppm)


f1 (ppm)


H
Me
MeO
35000
30000
25000
20000
15000
10000
5000
0
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

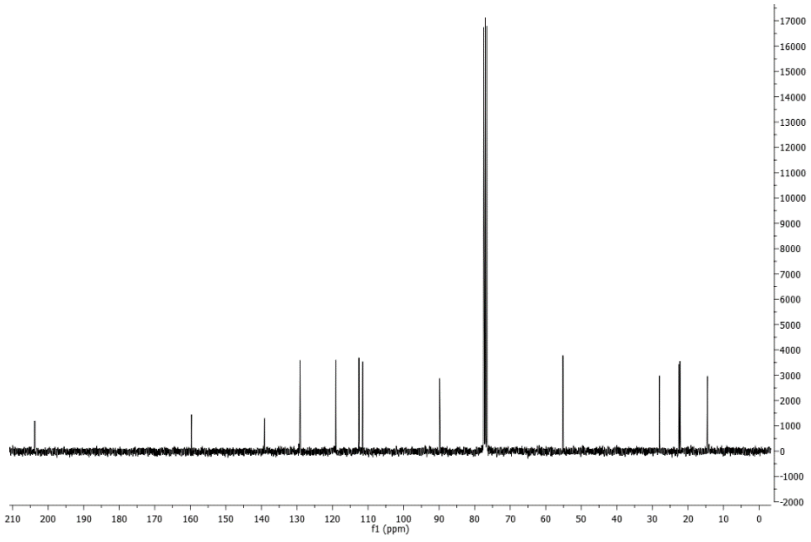
III-3v

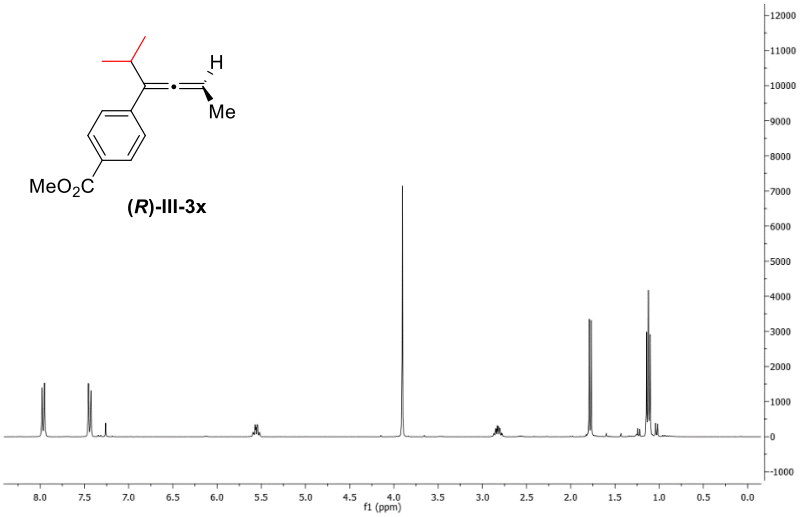

6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

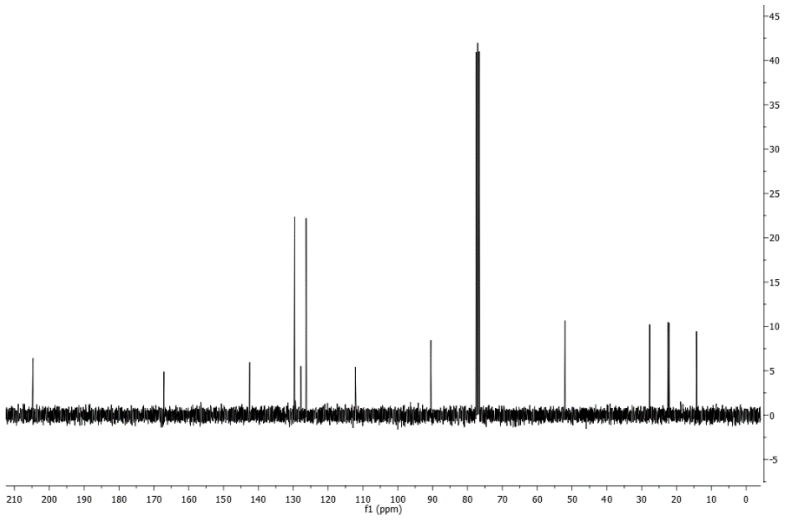

H
Me
MeO

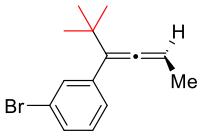
(*R*)-III-3w

20000
15000
10000
5000
0
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

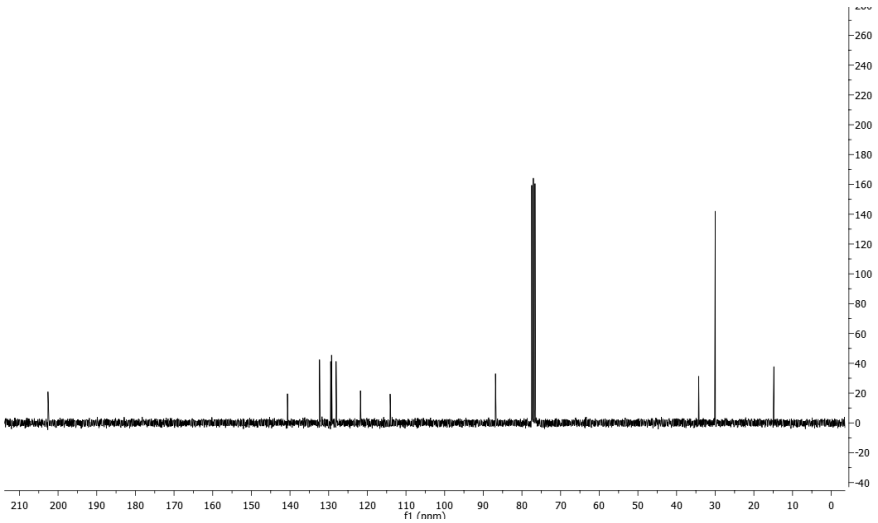

17000
16000
15000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
-2000
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

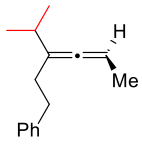

H
Me
MeO2C
(R)-III-3x
f1 (ppm)


f1 (ppm)



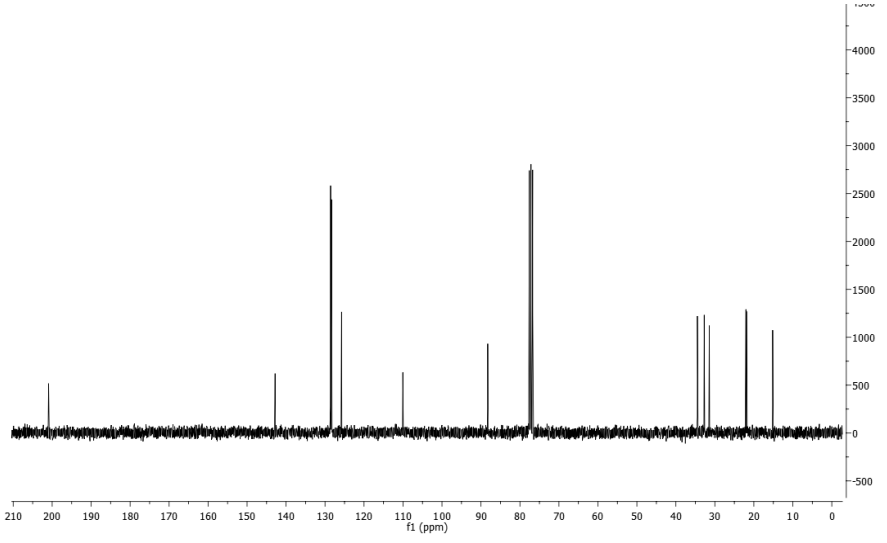
(*R*)-III-3y

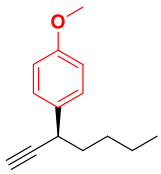



H
Me
Ph

(*S*)-III-3z

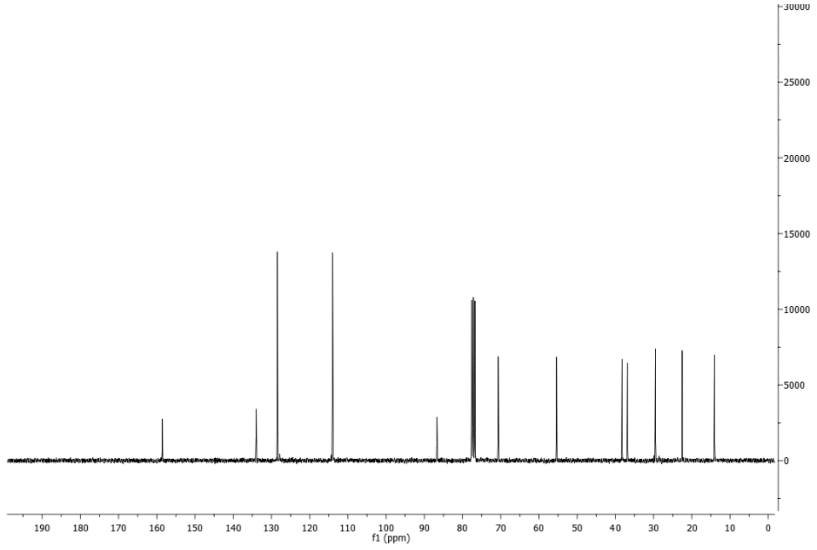
28000
26000
24000
22000
20000
18000
16000
14000
12000
10000
8000
6000
4000
2000
0
-2000
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

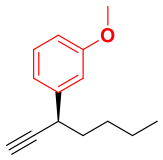

4000
3500
3000
2500
2000
1500
1000
500
0
-500
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


O

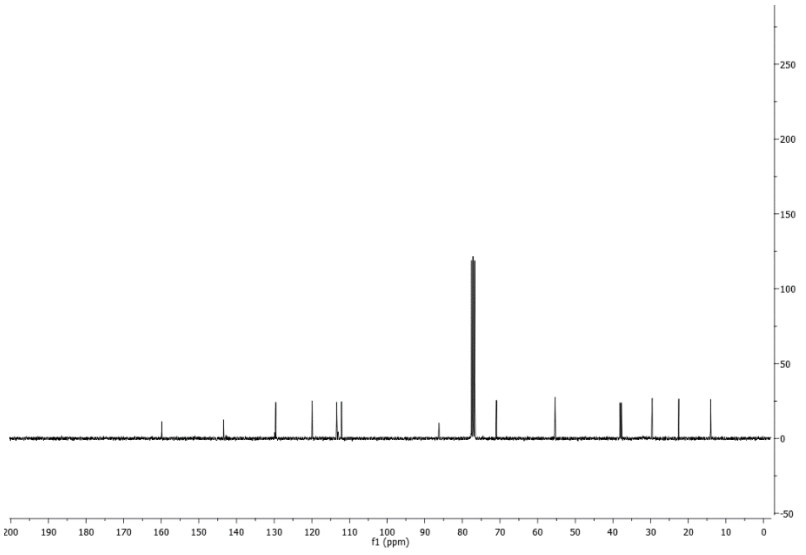
(*S*)-III-7x

4500
4000
3500
3000
2500
2000
1500
1000
500
0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

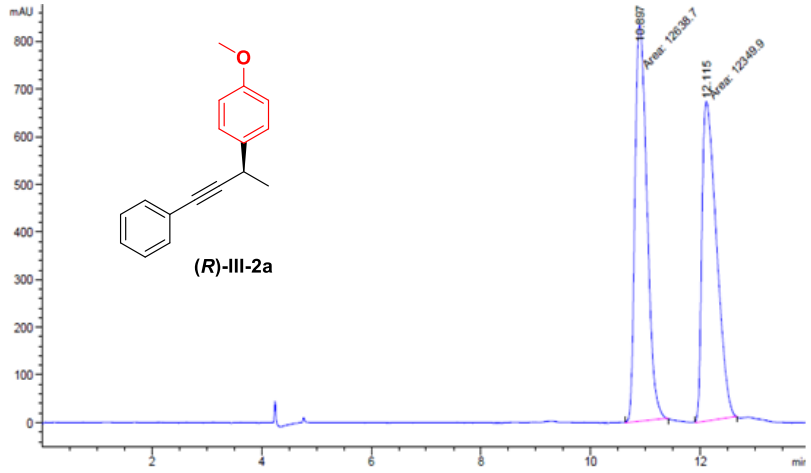

25000
20000
15000
10000
5000
0
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)



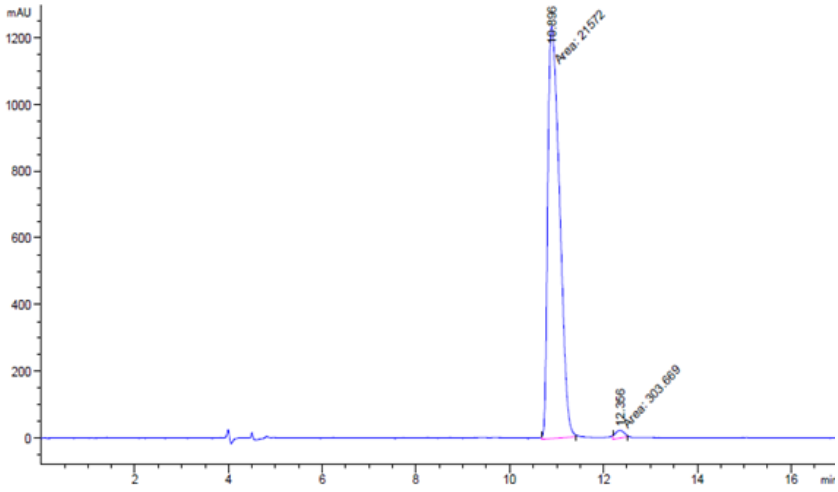
(*S*)-III-7y



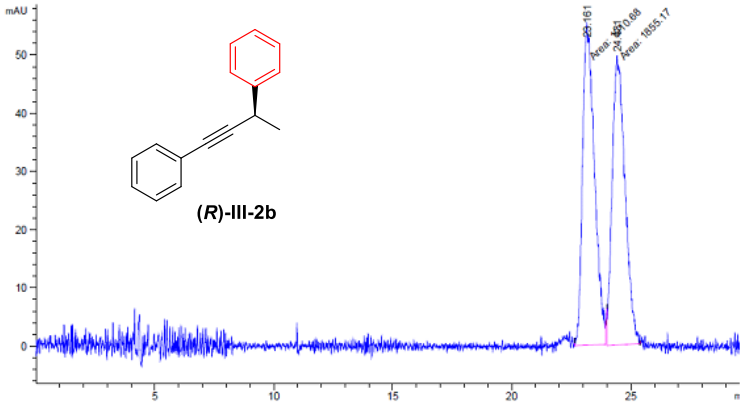
3.8. SFC Chromatograms



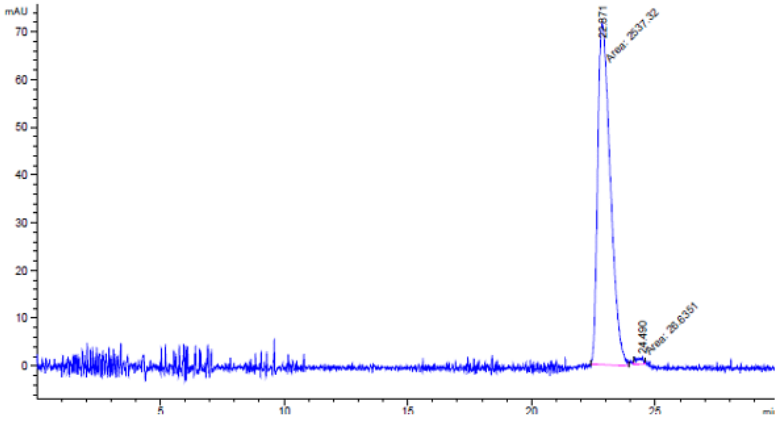
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.897	MM	0.2530	1.26387e4	832.54565	50.5780
2	12.115	MM	0.3069	1.23499e4	670.69751	49.4220



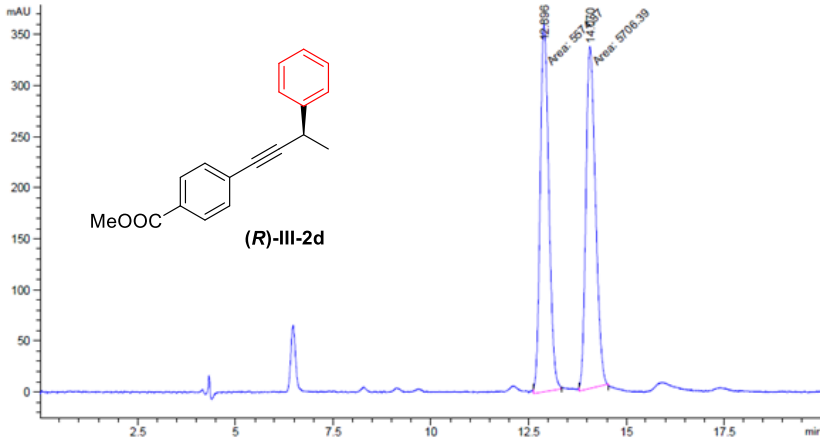
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.896	MM	0.2908	2.15720e4	1236.33911	98.6118
2	12.356	MM	0.2211	303.66855	22.88723	1.3882



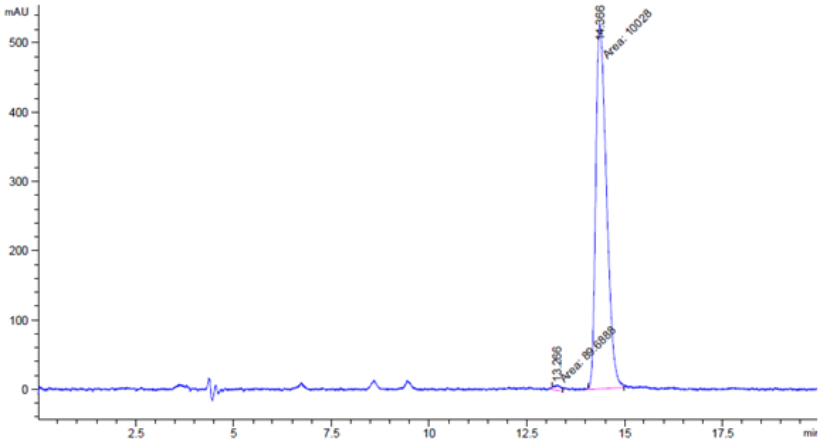
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	23.161	MM	0.5734	1910.67761	55.53371	50.7370
2	24.431	MM	0.6200	1855.17261	49.86818	49.2630



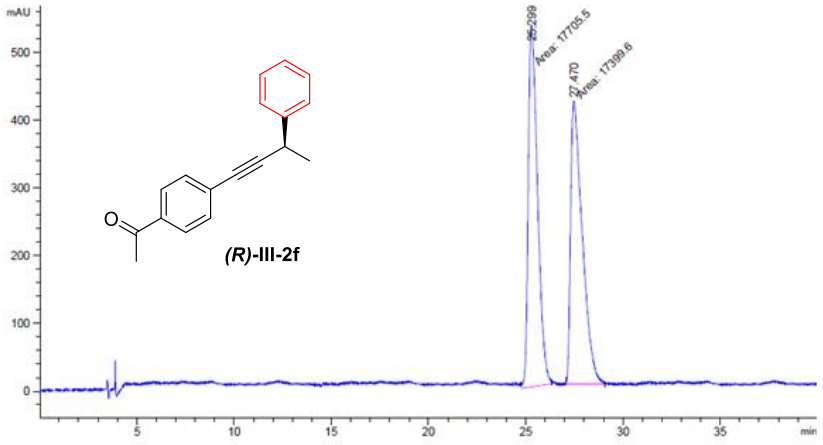
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	22.871	MM	0.5901	2537.32056	71.66963	98.9612
2	24.490	MM	0.3210	26.63508	1.38296	1.0388



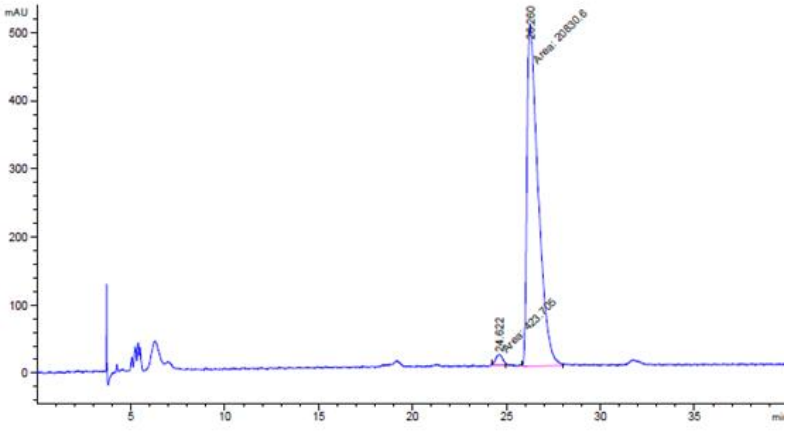
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.896	MM	0.2579	5574.36572	360.19241	49.4148
2	14.070	MM	0.2840	5706.38867	334.91086	50.5852



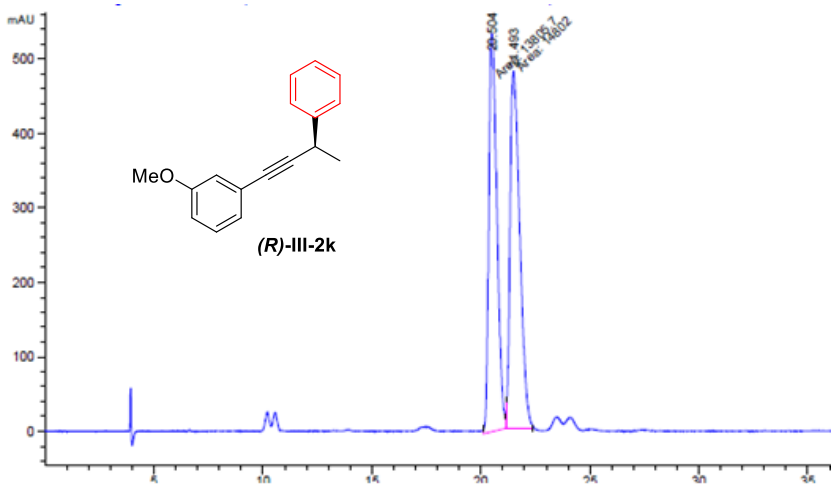
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.266	MM	0.1992	89.68884	7.50363	0.8865
2	14.366	MM	0.3175	1.00280e4	526.37775	99.1135



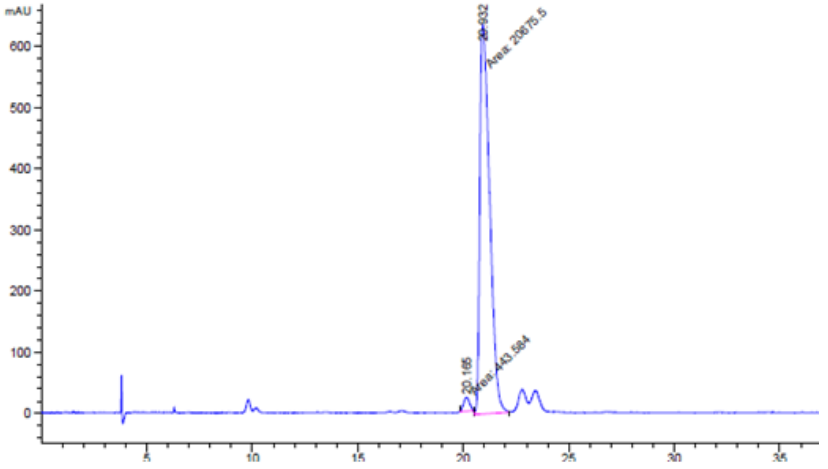
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	25.299	MM	0.5524	1.77055e4	534.21906	50.4357
2	27.470	MM	0.6948	1.73996e4	417.38214	49.5643



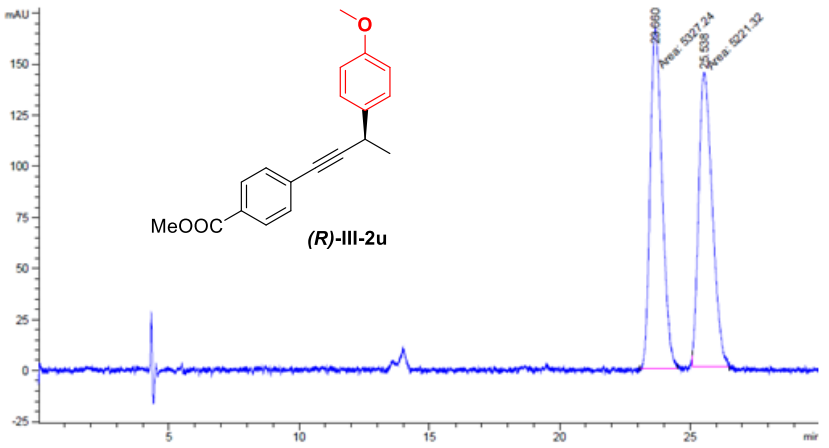
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	24.622	MM	0.4405	423.70480	16.02955	1.9935
2	26.260	MM	0.6907	2.08306e4	502.61490	98.0065



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	20.504	MM	0.4301	1.38057e4	534.96252	48.2587
2	21.493	MM	0.5145	1.48020e4	479.49701	51.7413



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	20.165	MM	0.3266	443.58377	22.63762	2.1004
2	20.932	MM	0.5405	2.06755e4	637.59009	97.8996



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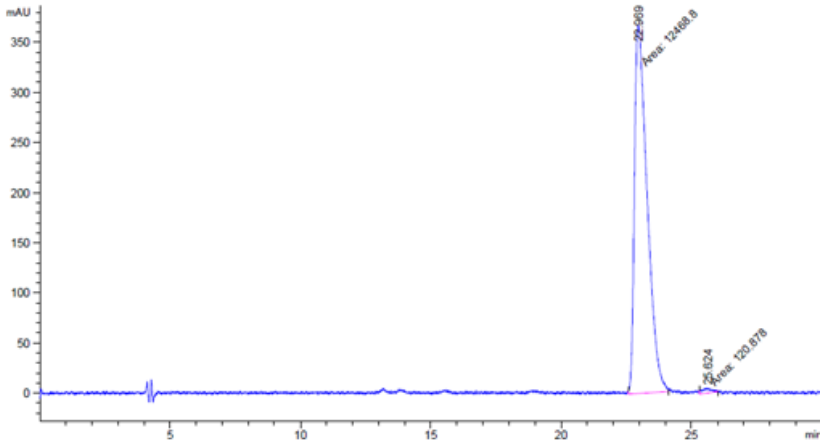
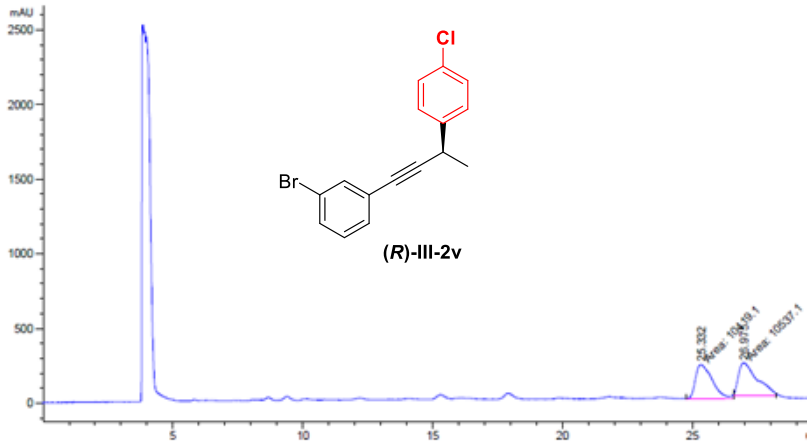
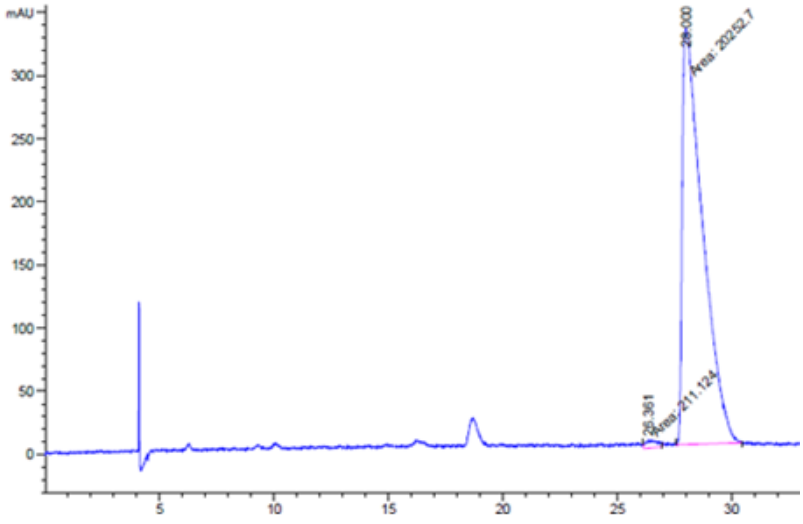
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	23.660	MM	0.5302	5327.23633	167.47346	50.5020
2	25.538	MM	0.6034	5221.32178	144.21445	49.4980



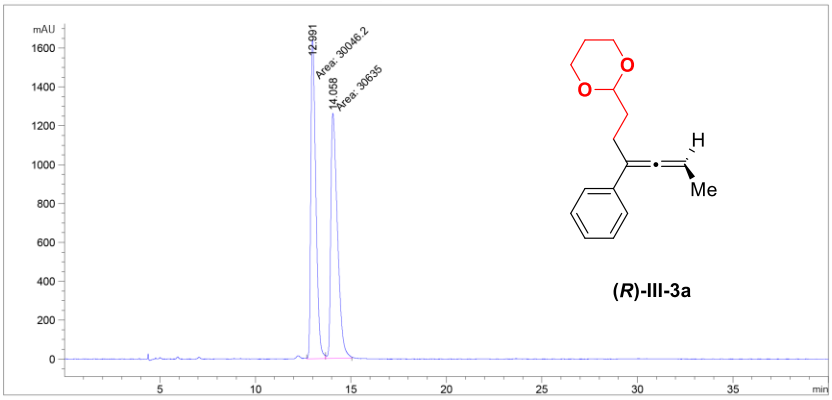
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	22.969	MM	0.5648	1.24688e4	367.96881	99.0399
2	25.624	MM	0.3905	120.87759	5.15934	0.9601



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	25.332	MM	0.7535	1.04191e4	230.45033	49.7184
2	26.975	MM	0.8186	1.05371e4	214.54501	50.2816



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	26.361	MM	0.5384	211.12447	6.53511	1.0317
2	28.000	MM	1.0237	2.02527e4	329.73666	98.9683



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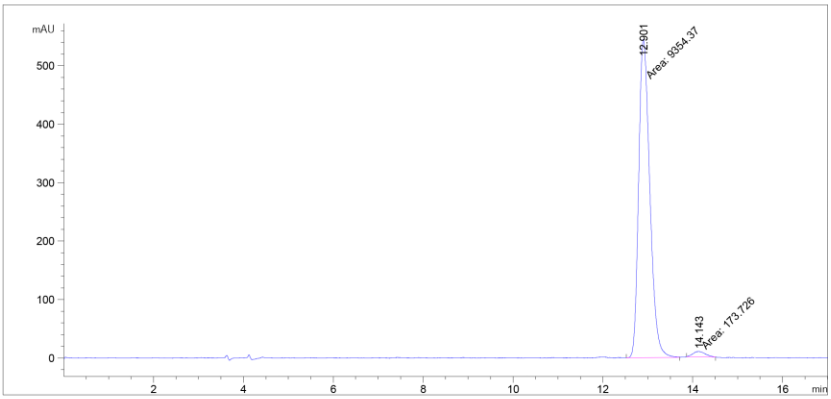
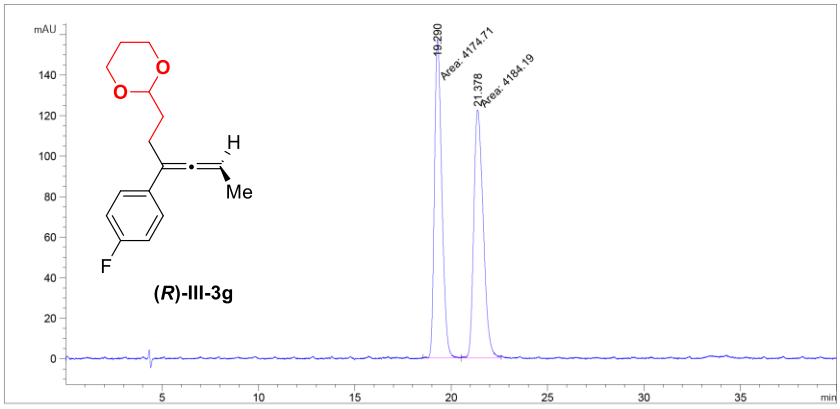
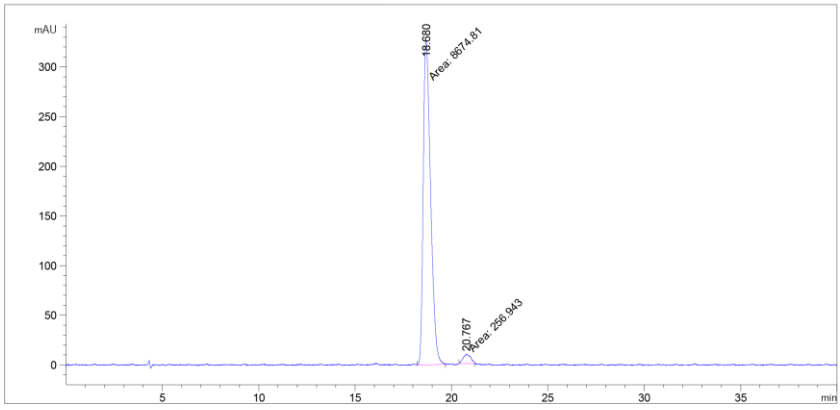
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.991	MF	0.3050	3.00462e4	1641.93506	49.5148
2	14.058	FM	0.4047	3.06350e4	1261.52649	50.4852



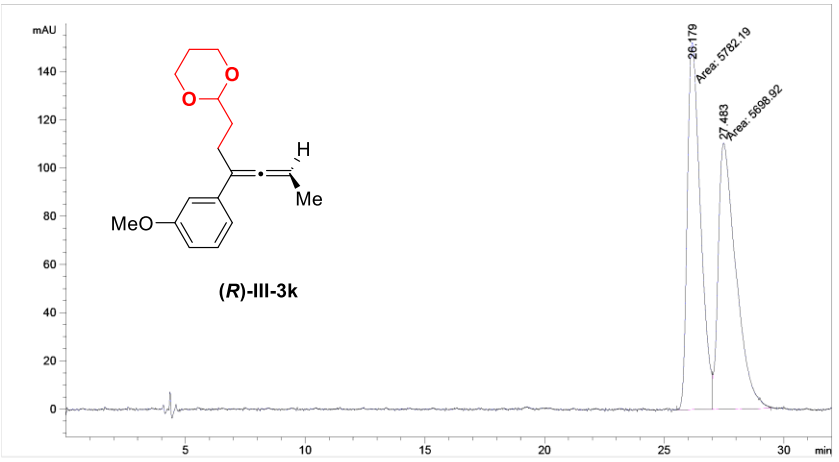
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.901	MM	0.2863	9354.37109	544.54041	98.1767
2	14.143	MM	0.3158	173.72585	9.16906	1.8233



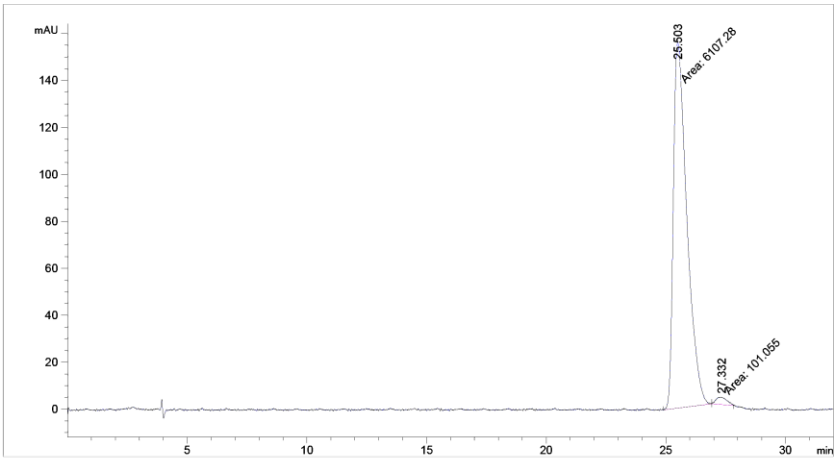
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.290	MF	0.4431	4174.71191	157.02931	49.9433
2	21.378	FM	0.5692	4184.19043	122.52728	50.0567



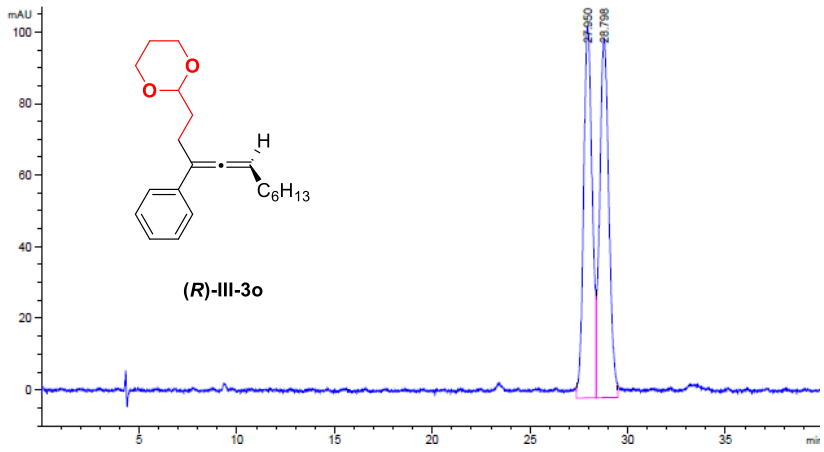
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.680	MM	0.4418	8674.80664	327.22290	97.1233
2	20.767	MM	0.4559	256.94296	9.39406	2.8767



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	26.179	MF	0.6328	5782.19043	152.28716	50.3626
2	27.483	FM	0.8602	5698.92236	110.42137	49.6374



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	25.503	MM	0.6536	6107.28223	155.73372	98.3723
2	27.332	MM	0.5117	101.05537	3.29147	1.6277



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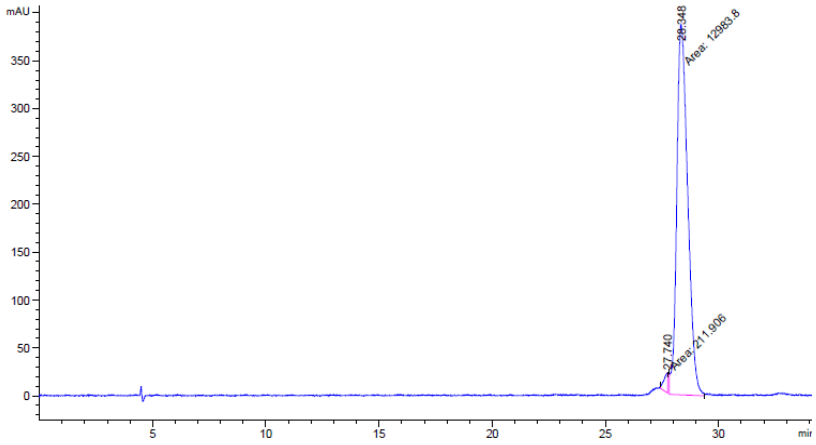
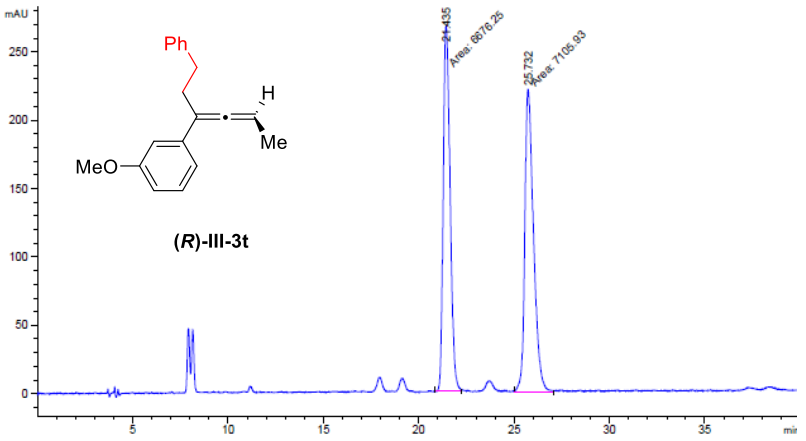
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	27.950	VV	0.3614	3168.53613	103.70884	49.0808
2	28.798	VV	0.3866	3287.21826	100.50181	50.9192

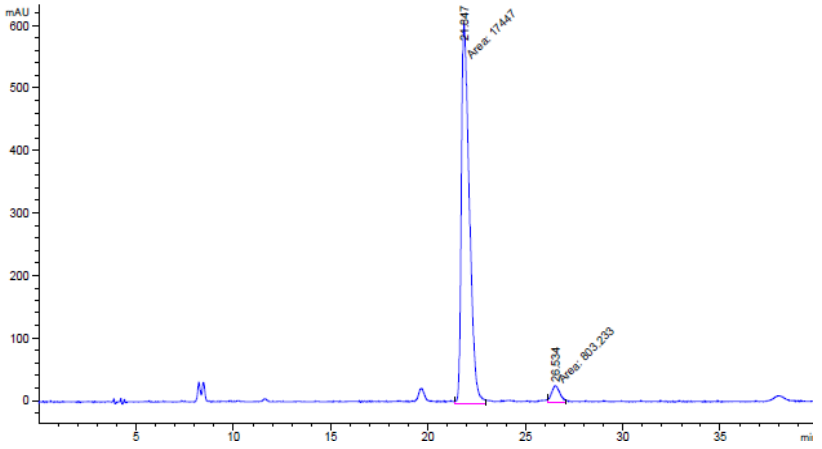


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	27.740	MM	0.1686	211.90648	20.94443	1.6059
2	28.348	MM	0.5587	1.29838e4	387.30658	98.3941

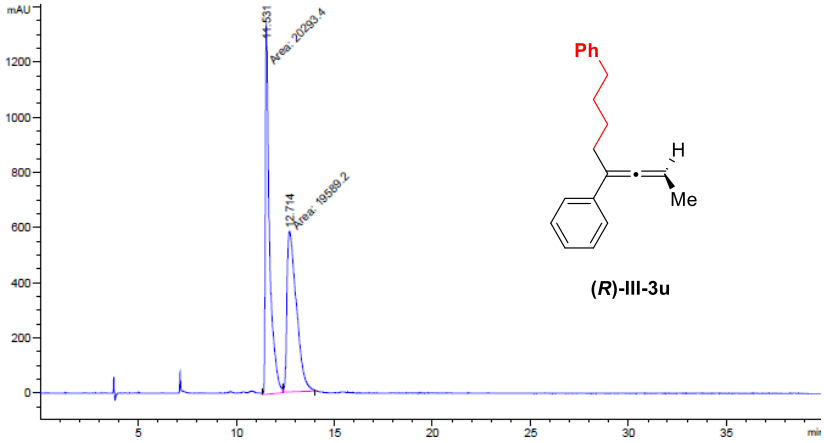


(*R*)-III-3t

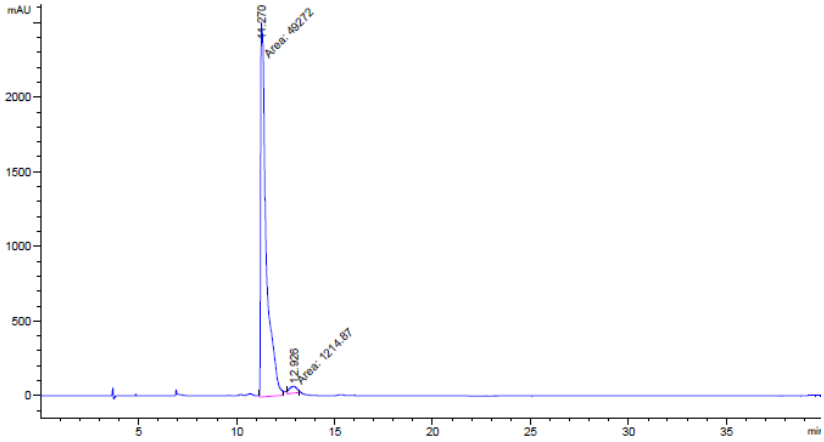
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	21.435	MM	0.4164	6676.24658	267.22153	48.4412
2	25.732	MM	0.5333	7105.93164	222.06223	51.5588



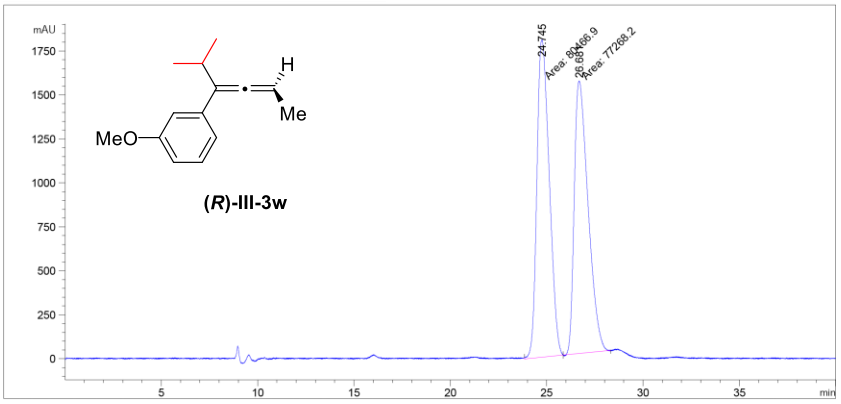
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	21.847	MM	0.4784	1.74470e4	607.79889	95.5988
2	26.534	MM	0.5051	803.23254	26.50383	4.4012



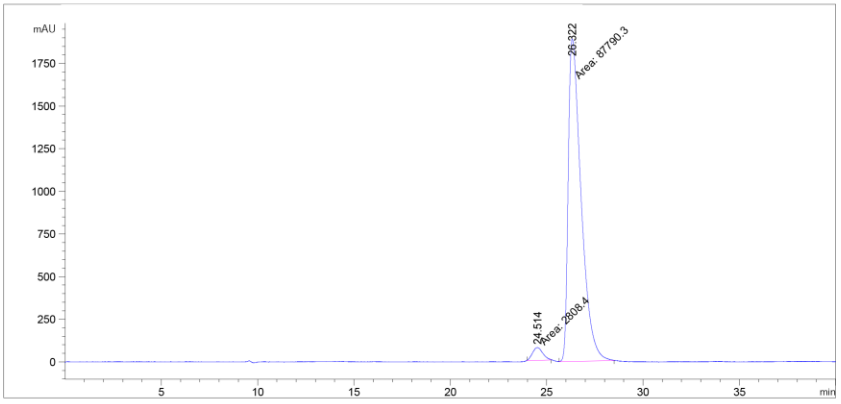
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.531	MM	0.2510	2.02934e4	1347.72913	50.8827
2	12.714	MM	0.5616	1.95892e4	581.32056	49.1173



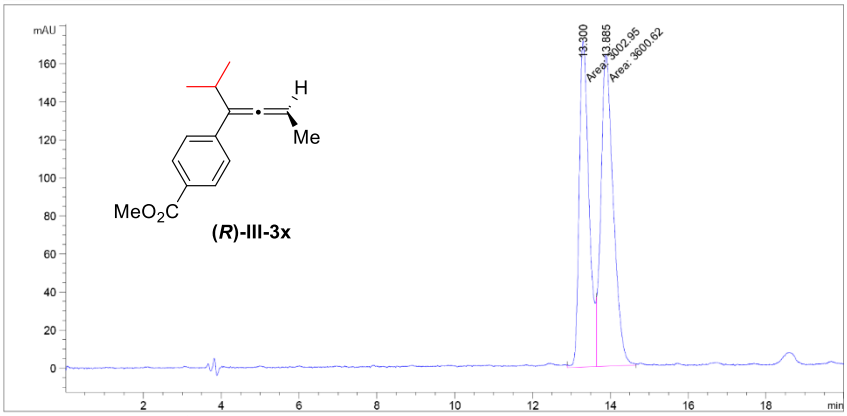
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.270	MM	0.3278	4.92720e4	2504.91699	97.5937
2	12.926	MM	0.4479	1214.87415	45.20641	2.4063



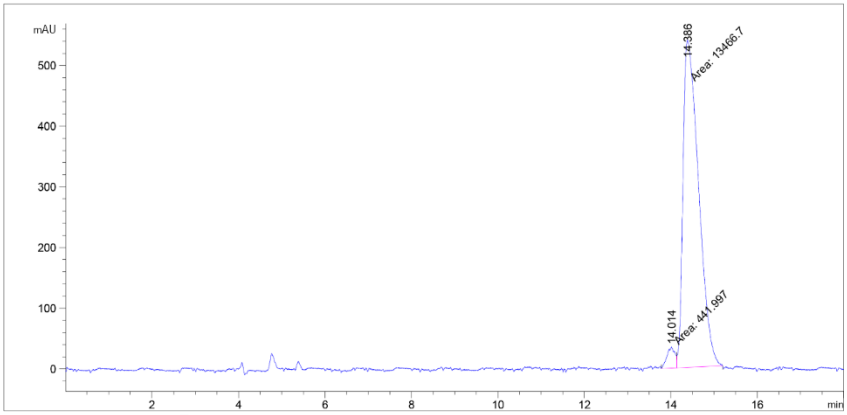
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	24.745	MF	0.7434	8.04669e4	1804.02307	51.0139
2	26.681	FM	0.8309	7.72682e4	1549.91821	48.9861



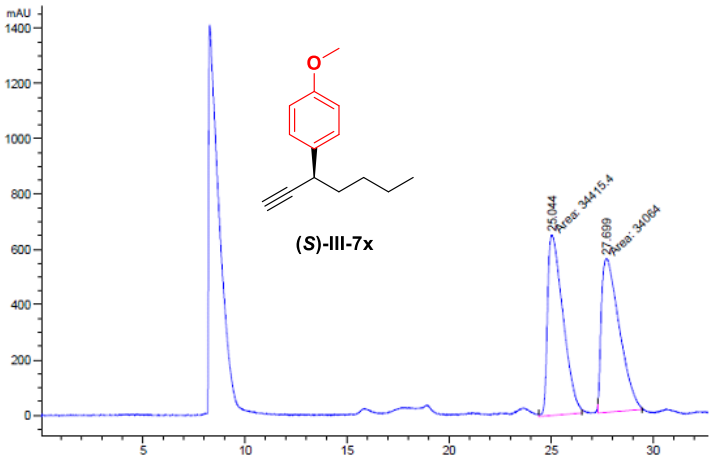
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	24.514	MM	0.6154	2808.39893	76.06504	3.0998
2	26.322	MM	0.7746	8.77903e4	1888.90845	96.9002



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.300	MF	0.2919	3002.95361	171.43990	45.4747
2	13.885	FM	0.3656	3600.61670	164.14279	54.5253

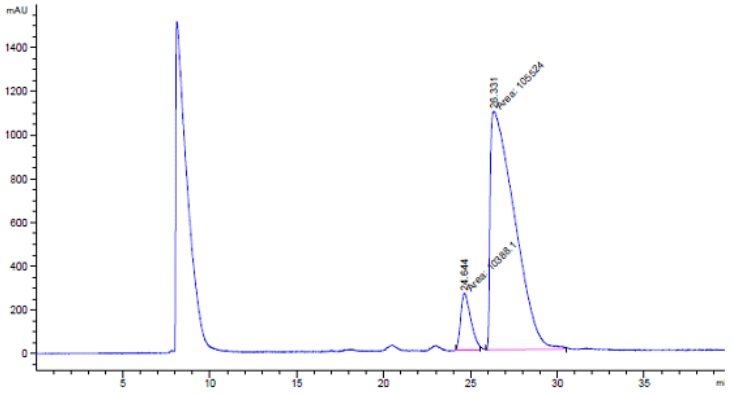


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.014	MF	0.2123	441.99741	34.69642	3.1778
2	14.386	FM	0.4161	1.34667e4	539.39026	96.8222

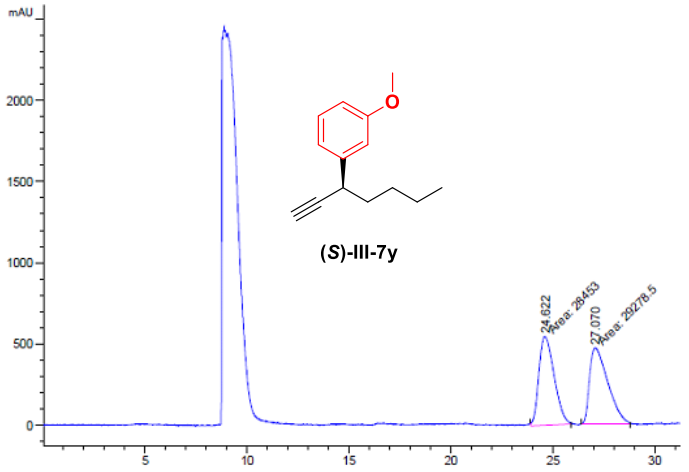


(*S*)-III-7x

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	25.044	MM	0.8797	3.44154e4	652.04083	50.2566
2	27.699	MM	1.0208	3.40640e4	556.14600	49.7434

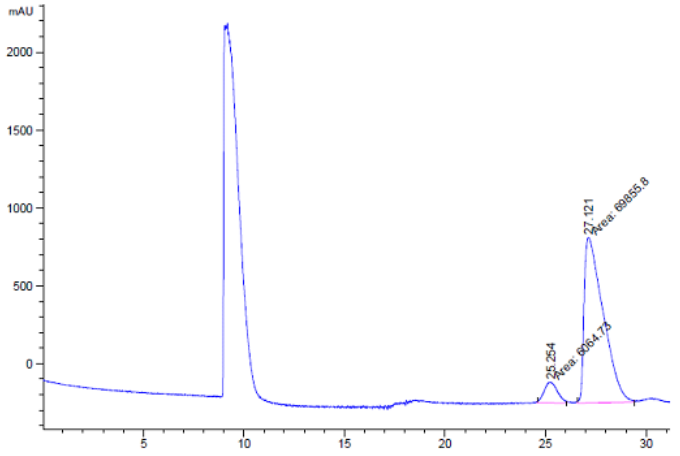


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	24.644	MM	0.6704	1.03881e4	258.24075	8.9620
2	26.331	MM	1.6132	1.05524e5	1090.21948	91.0380



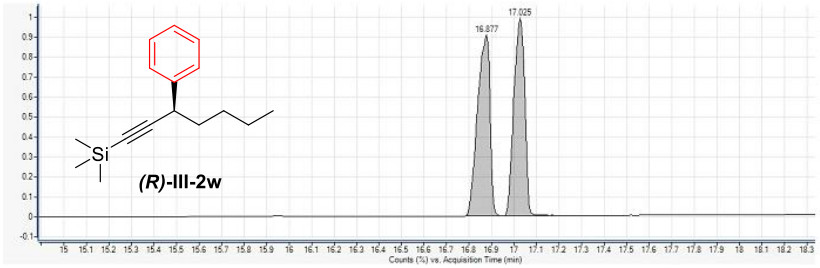
(*S*)-III-7y

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	24.622	MM	0.8677	2.84530e4	546.52899	49.2850
2	27.070	MM	1.0399	2.92785e4	469.25476	50.7150



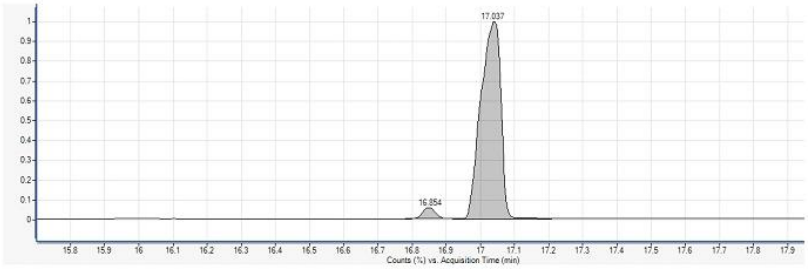
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	25.254	MM	0.7596	6064.72656	133.07111	7.9883
2	27.121	MM	1.0955	6.98558e4	1062.77173	92.0117

3.9. GC-MS Chromatograms



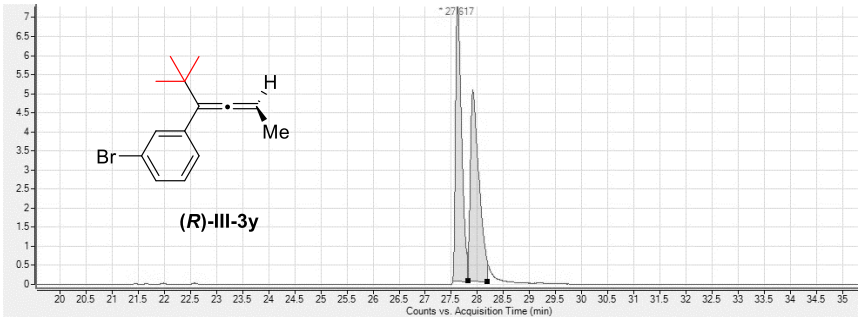
Integration Peak List

Peak	Start	RT	End	Height	Area	Area %
1	16.785	16.877	16.951	39400520.56	150507725.1	100
2	16.951	17.025	17.191	43045245.34	142983500.5	95

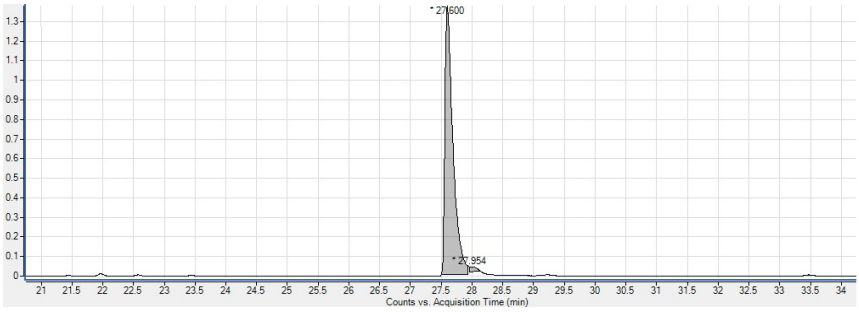


Integration Peak List

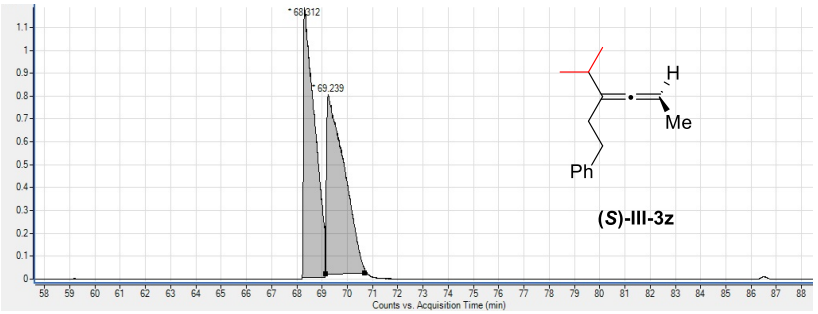
Peak	Start	RT	End	Height	Area	Area %
1	16.797	16.854	16.923	3784811.23	15001365.27	7.31
2	16.951	17.037	17.1	50349653.67	205333335	100



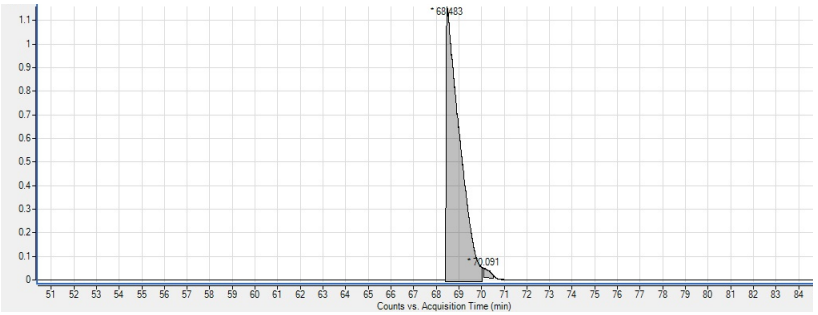
Peak	Start	End	RT	Area	Area %	Height
1	27,526	27,812	27,617	57815039,65	99,01	7188815,72
2	27,823	28,195	27,909	58391186,5	100	5013215,34



Peak	Start	End	RT	Area	Area %	Height
1	27,502	27,94	27,6	125290537,7	100	13710111,58
2	27,954	28,13	28	1953058,44	1,56	272926,73



Peak	Start	End	RT	Area	Area %	Height
1	68,214	69,124	68,312	36503417,47	95,12	1180333,3
2	69,136	70,686	69,239	38378069,77	100	785301,23



Peak	Start	End	RT	Area	Area %	Height
1	68,426	70,034	68,483	46915341,96	100	1154087,64
2	70,086	70,715	70,091	799440,78	1,7	38877,59

Chapter 4

STEREOSPECIFIC SYNTHESIS OF 1,5-DIENES THROUGH AN ALLYL-ALLYL CROSS-COUPLING STRATEGY.

4. STEREOSPECIFIC PALLADIUM-CATALYZED ALLYL-ALLYL CROSS-COUPLING OF ALLYLIC CARBONATES AND AMMONIUM SALTS.

4.1. Background.

4.1.1. Allyl-Allyl Cross-Coupling.

1,5-dienes are a prevalent structure in many important biologically active molecules (**Figure *4-1***).[1] As a common terpene structure, plays a key role in nature.

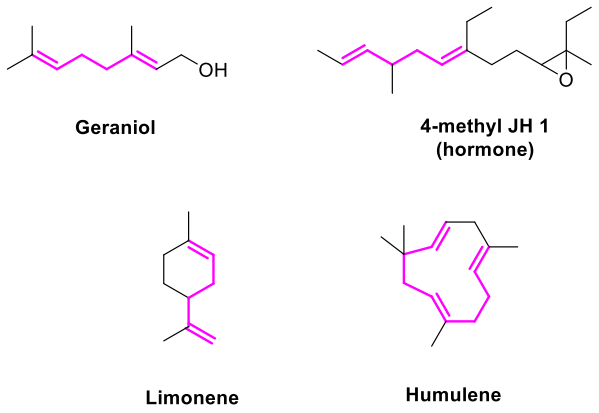
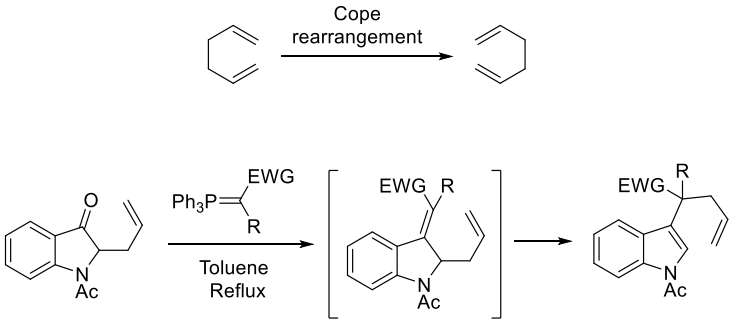


Figure 4-1: Common natural products with 1,5-dienes in their structure.

[1] Breitmaier, E. *Terpenes: Flavors, Fragrances, Pharmaca, Pheromones*, Wiley-VCH, Weinheim, 2006.

Moreover, 1,5-dienes are versatile synthetic intermediates that can be used for the preparation of a wide range of compounds. One of the classical reaction involving 1,5-dienes is the Cope rearrangement.[2] This transformation is a sigmatropic reaction which have been known for nearly eight decades and since its discovery, many variations have been reported (**Scheme *4-1***).[3]



Scheme 4-1: Cope rearrangement.

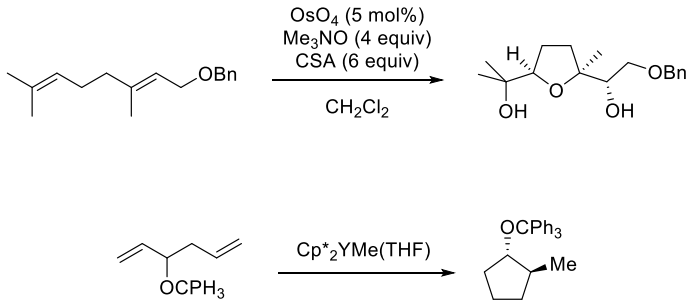
Other well-known transformations are the oxidative cyclization of 1,5-dienes to obtain furanyl rings (**Scheme *4-2***, top),[4] cycloisomerization

[2] Cope, A.C.; Hardy, E.M. *J. Am. Chem. Soc.* **1940**, *62*, 441-444. For a specific example see: Kawasaki, T.; Nonaka, Y.; Watanabe, K.; Ogawa, A.; Higuchi, K.; Terashima, R.; Masuda, K.; Sakamoto, M. *J. Org. Chem*. **2001**, *66*, 1200-1204.

[3] For a review see: Lutz, R.P. *Chem. Rev*. **1984**, *3*, 205-247. For more recent examples: a) Overman, L.E.; Knoll, F.M. *J. Am. Chem. Soc.* **1980**, *102*, 865-867. b) Felix, R.J.; Weber, D.; Gutierrez, O.; Tantillo, D.J.; Gagne, M.R. *Nature Chemistry* **2012**, *4*, 405-409.

[4] a) Antonsson, T.; Moberg, C.; Tottie, L. *J. Org. Chem.* **1989**, *54*, 4914-4929. c) Brown, R.C.D.; Keily, J.F. *Angew. Chem. Int. Ed.* **2001**, *40*, 4496-4498. d) Donohoe, T.J.; Butterworth, S.

reactions (**Scheme *4-2***, bottom)[5] and the selective functionalization of both olefins.



Scheme 4-2: Utility of 1,5-dienes.

One of the most straightforward strategies to prepare 1,5-dienes is the metal-catalyzed allyl-allyl cross-coupling reaction between two different allylic partners. Different transition metals have been used to catalyze this transformation, including stereoselective variants. In those cases, the products are enantioenriched 1,5 dienes with one or more stereocenters.[6] In

[5] a) Molander, G.A.; Hoberg, J.O. *J. Am. Chem. Soc.* **1992**, *114*, 3123-3125. b) Kisanga, P.; Goj, L.A.; Widenhoefer, R.A. *J. Org. Chem.* **2001**, *66*, 635-637.

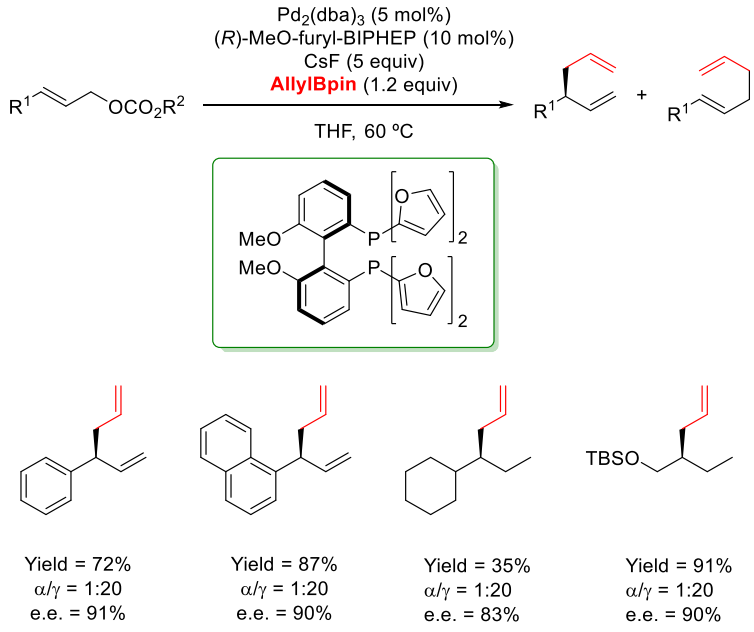
[6] a) Trost, B.M.; Keinan, E. *Tetrahedron Lett.* **1980**, *21*, 2595-2598. b) Godschalx, J.; Stille, J.K. *Tetrahedron Lett.* **1980**, *21*, 2599-2602. c) Keinan, E.; Peretz, M. *J. Org. Chem.* **1983**, *48*, 5302-5309. d) Stille, J.K. *Angew. Chem. Int. Ed.* **1986**, *25*, 508-524. e) Sofia, A.; Karlstrom, E.; Backvall, J.E. *Chem. Eur. J.* **2001**, *7*, 1981-1989. f) Mendez, M.; Cuerva, J.M.; Gomez-Bengoa, E.; Cardenas, D.J.; Echavarren, A.M. *Chem. Eur. J.* **2002**, *8*, 3620-3628. g) Mendez, M.; Echavarren, A.M.*Eur. J. Org. Chem.* **2002**, 15-28. h) Porcel, S.; Lopez-Carrillo, V.; Garcia-Yebra, C.; Echavarren, A.M. *Angew. Chem. Int. Ed.* **2008**, *47*, 1883-1886. i) Sumida, Y.; Hayashi, S.; Hirano, K.; Yorimitsu, H.; Oshima, K. *Org. Lett.* **2008,** *10*, 1629-1632.

this section, selected examples of enantioselective and stereospecific allyl-allyl cross-coupling will be discussed.

4.1.2. Enantioselective Allyl-Allyl Cross-Coupling.

In 2010, Morken and co-workers reported the first enantioselective allyl-allyl cross-coupling between allylic carbonates and allyl boronates (**Scheme *4*-*3***).[7] The branched product was formed as a single regioisomer with high levels of stereocontrol. They observed that regioselectivity was dependent of the bite angle of the ligand, being the best a chiral ligand with a small bite angle.[8]

[7] Zhang, P.; Brozek, L.A.; Morken, J.P. *J. Am. Chem. Soc.* **2010**, *132*, 10686-10688.
[8] Ardolino, M.J.; Morken, J.P. *Tetrahedron*, **2015**, *71*, 6409-6413.



Scheme 4-3: Palladium-catalyzed enantioselective allyl-allyl cross-coupling.

Although the reaction might have occurred by an outer-sphere attack of the allylboronate to a η^3-allyl palladium complex,[9] based on mechanistic experiments, they proposed an inner-sphere 3,3-reductive elimination pathway for the reaction,[10] as proposed by Echevarren[11] and Espinet.[12] First,

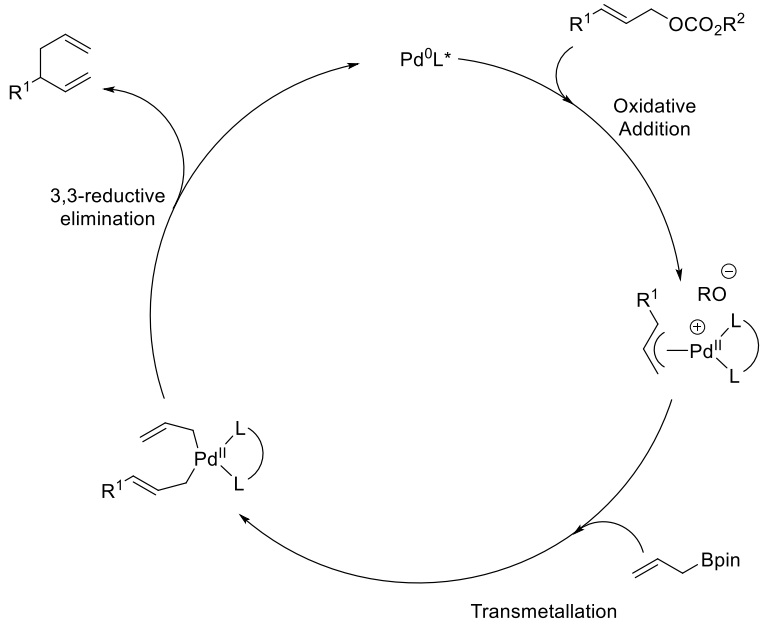
[9] a) Trost, B. M.; Keinan, E. *Tetrahedron Lett.* **1980**, *21*, 2595-2598. b) Godschalx, J.; Stille, J. K. *Tetrahedron Lett.* **1980**, *21*, 2599-2602. c) Flegeau, E. F.; Schneider, U.; Kobayashi, S. *Chem. Eur. J.* **2009**, *15*, 12247-12254. d) Jiminéz-Aquino, A.; Flegeau, E. F.; Schneider, U.; Kobayashi, S. *Chem. Commun.* **2011**, *47*, 9456-9458.

[10] Ardolino, M.J.; Morken, J.P. *J. Am. Chem. Soc.* **2014**, *136*, 7092-7100.

[11] a) Méndez, M.; Cuerva, J. M.; Gómez-Bengoa, E.; Cárdenas, D. J.; Echavarren, A. M. *Chem. Eur. J.* **2002**, *8*, 3620-3628. b) Cárdenas, D. J.; Echavarren, A. M. *New J. Chem.* **2004**, *28*, 338-347.

[12] a) Pérez-Rodríguez, M.; Braga, A. A. C.; Garcia-Melchor, M.; Pérez-Temprano, M. H.; Casares, J. A.; Ujaque, G.; de Lera, A. R.; Maseras, F.; Álvarez, R.; Espinet, P. *J. Am. Chem. Soc.* **2009**, *131*, 3650-3657. b) Pérez-Rodríguez, M.;

there must be an oxidative addition of the carbonate to the palladium(0) complex to form a η^3-allyl palladium complex, that would explain that the result was the same using either the branched or the linear allylic carbonate. Then, after the transmetalation step, the coordination of the small-bite bidentate phosphine would cause the two allyl group to adopt a η^1 bonding mode that would favor the 3,3-reductive elimination pathway to produce the desired product (**Scheme *4-4***).

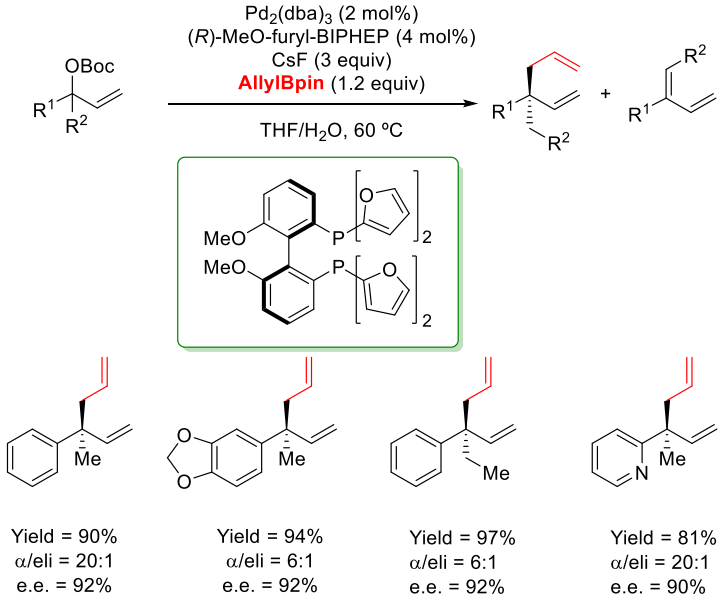


Scheme 4-4: Proposed mechanism for the palladium-catalyzed allyl-allyl cross-coupling via a 3,3-reductive elimination pathway.

A year later, the same group reported a similar transformation, using tertiary allylic carbonates as starting allylic electrophiles. Using the same

Braga, A. A. C.; de Lera, A. R.; Maseras, F.; Álvarez, R.; Espinet, P. *Organometallics* **2010**, *29*, 4983-4991.

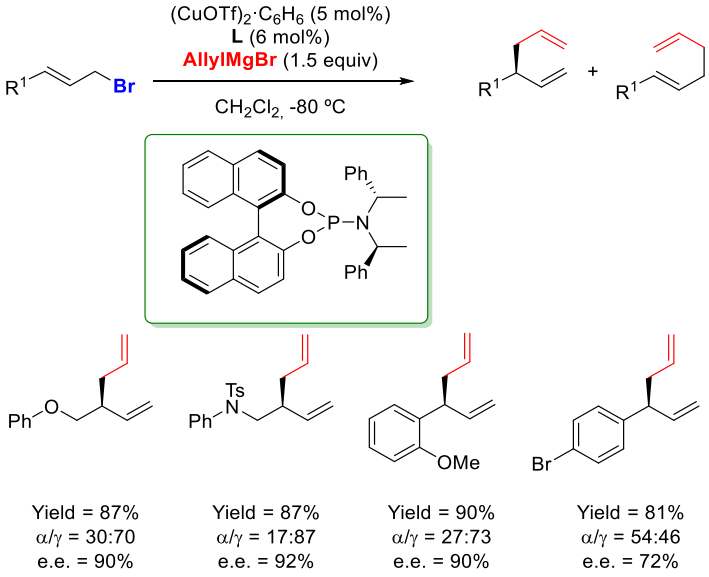
chiral ligand as before, they prepared compounds with all-carbon quaternary centers from racemic substrates with excellent results (**Scheme *4-5***).[13] The transformation was not trivial, because an interconversion between the two possible π-allyl-palladium intermediates through a hindered tertiary η^1-allylpalladium intermediate was needed. One of the drawbacks of this report was that a considerable amount of β-hydride elimination product was formed in some cases. In the same year they reported a similar transformation using internal allylboronates with excellent diastereo- and enantioselectivities.[14]



Scheme 4-5: Enantioselective allyl-allyl cross-coupling of quaternary carbonates.

[13] Zhang, P.; Kyne, R.E.; Morken, J.P. *J. Am. Chem. Soc.* **2011**, *133*, 9716-9719.
[14] Brozek, L.A.; Ardolino, M.J.; Morken, J.P. *J. Am. Chem. Soc.* **2011**, *133*, 16778-16781.

In 2013, Feringa and co-workers reported the first copper-catalyzed allyl-allyl cross-coupling. They obtained high levels of regio- and enantioselectivity using a chiral phosphoramidite ligand along with a copper(I) salt (**Scheme *4-6***).[15] They used readily available allyl bromides and allylmagnesium bromide to obtain enantiomerically enriched 1,5-dienes. They proposed that the mechanism for this transformation was similar to the copper-catalyzed asymmetric allylic alkylation (Cu-AAA).[16]

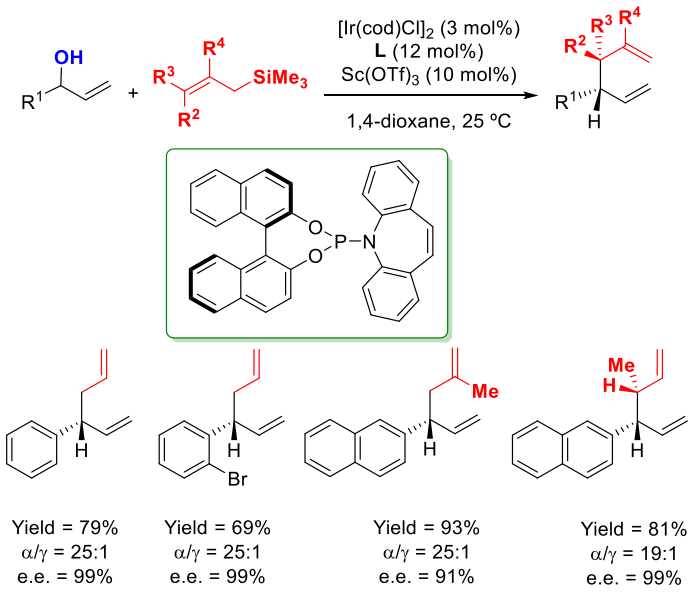


Scheme 4-6: Enantioselective copper-catalyzed allyl-allyl cross-coupling.

Carreira and co-workers added an elegant contribution to this field. They reported the enantioselective cross-coupling between unprotected allylic

[15] Hornillos, V.; Perez, M.; Fañanas-Mastral, M.; Feringa, B.L. *J. Am. Chem. Soc.* **2013**, *135*, 2140-2143.
[16] Yoshikai, N.; Nakamura, E. *Chem. Rev.* **2012**, *112*, 2339-2372.

alcohols and allylsilanes catalyzed by iridium (**Scheme *4-7***).[17] Chiral phosphoramidites were this time the ligand of choice. They applied their methodology to the synthesis of a pyrethroid insecticide. Later, Yang and coworkers reported a similar procedure using allylboronates as nucleophiles.[18]

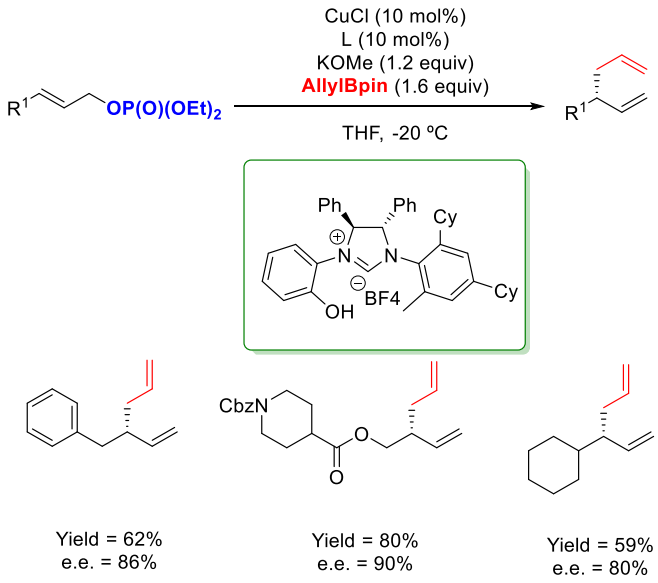


Scheme 4-7: Enantioselective iridium-catalyzed allyl-allyl cross-coupling.

In 2016, Sawamura and co-workers reported the cross coupling between (*Z*)-allylic phosphonates and allylboronates catalyzed by a Cu-NHC chiral

[17] Hamilton, J.Y.; Hauser, N.; Sarlah, D.; Carreira, E.M. *Angew. Chem. Int. Ed.* **2014**, *53*, 10759-10762.
[18] Zheng, Y.; Yue, B.B.; Wei, K.; Yang, Y.R. *Org. Lett.* **2018**, *20*, 8035-8038.

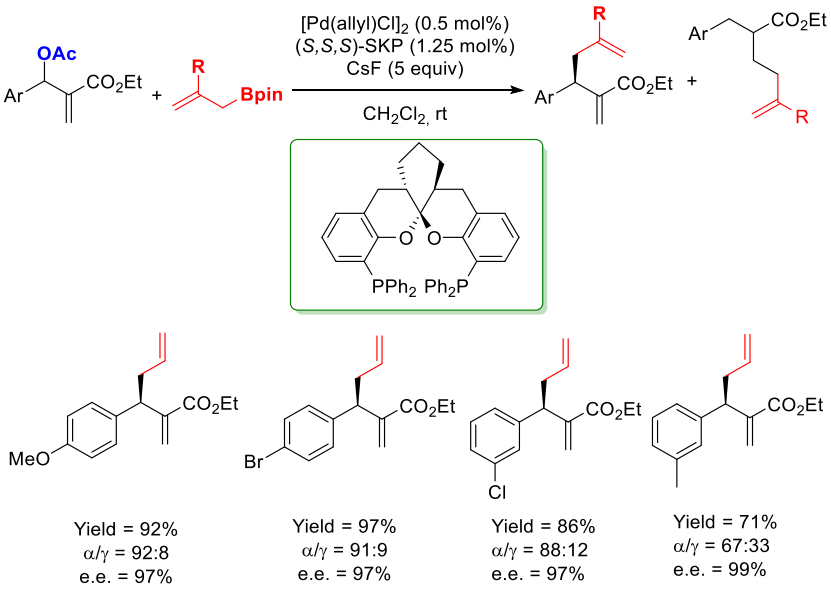
complex. The reaction was completely γ-regioselective and the products were obtained with moderate to good stereoselectivities (**Scheme *4-8***).[19]



Scheme 4-8: Copper-catalyzed enantioselective allyl-allyl cross-coupling.

Recently, Wang, Ding and co-workers reported a palladium-catalyzed allylic allylation of Morita-Baylis-Hillman adducts. Using a chiral spiroketal-based phosphine and allylic boronates as coupling partners, they obtained high regio- and enantioselectivities (**Scheme *4-9***).[20] As Morken's group, they proposed an inner-sphere 3,3'-reductive elimination as key step in the mechanism.

[19] Yasuda, Y.; Ohmiya, H.; Sawamura, M. *Angew. Chem. Int. Ed.* **2016**, *55*, 10816-10820.
[20] Wang, X.; Wang, X.; Han, Z.; Wang, Z.; Ding, K. *Angew. Chem. Int. Ed.* **2017**, *56*, 1116-1119.

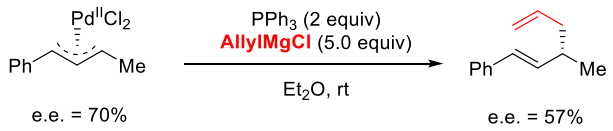


Scheme 4-9: Enantioselective allyl-allyl cross-coupling of Morita-Baylis-Hillman adducts.

4.1.3. Stereospecific Allyl-Allyl Cross-Coupling.

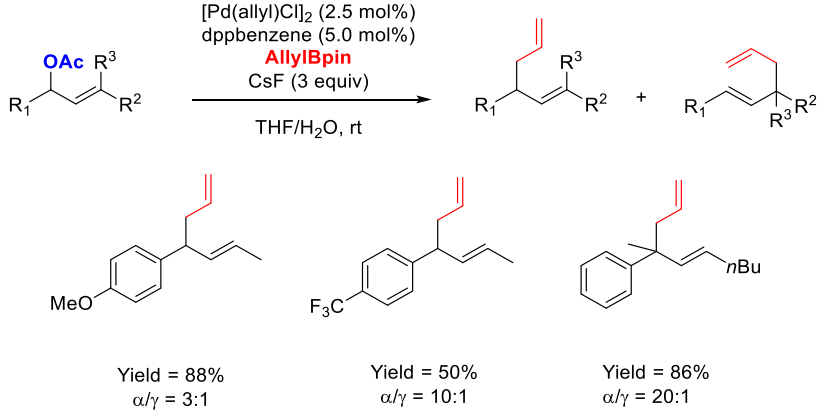
In a pioneering work, Hayashi and co-workers reported the reaction of enantiomerically enriched π-allylpalladium complex with various nucleophiles. One of the examples involved the stereospecific coupling with allylmagnesium chloride, which reacted with retention of the stereochemistry (**Scheme *4-10***).[21] The chirality transfer for this transformation was only moderate and they proposed an inner-sphere mechanism for the reaction.

[21] Hayashi, T.; Konishi, M.; Kumada, M. *J. Chem. Soc., Chem. Commun*. **1984**, 107-108.



Scheme 4-10: Stereospecific reaction between π-allylpalladium complex and allylmagnesium chloride.

The use of internal allyl electrophiles in stereospecific allyl-allyl cross-coupling reactions is much less developed. In a pioneering work, Morken and co-workers reported the palladium-catalyzed allyl-allyl cross-coupling of internal allylic acetates with allylboronates (**Scheme *4-11***).[22] They could not control the regioselectivity with disubstituted allyl acetates. Better regiocontrol was observed with trisubstituted allyl acetates.

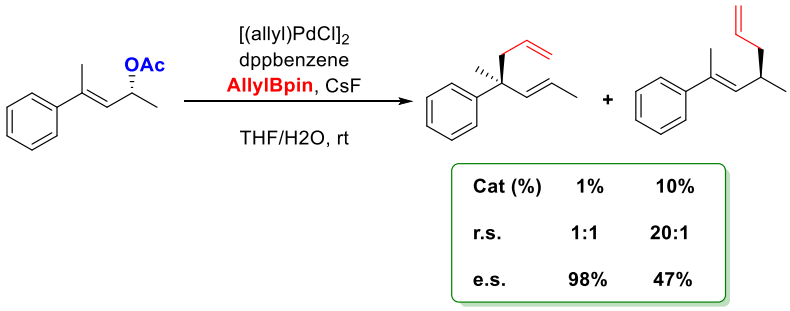


Scheme 4-11: Allyl-allyl cross-coupling of internal allylic acetates.

They studied the chirality transfer starting from enantioenriched allylic acetates. The catalyst loading had an influence in both the stereospecificity

[22] Le, H.; Batten, A.; Morken, J.P. *Org. Lett.* **2014**, *16*, 2096-2099.

and the regioselectivity, with opposite effects. Low catalyst loading afforded excellent stereospecificity but low regioselectivity. On the other hand, higher catalyst loading control the regioselectivity, but is detrimental for the chirality transfer (**Scheme *4-12***). In all cases they isolated the product along an unknown quantities of β-hydride elimination product.



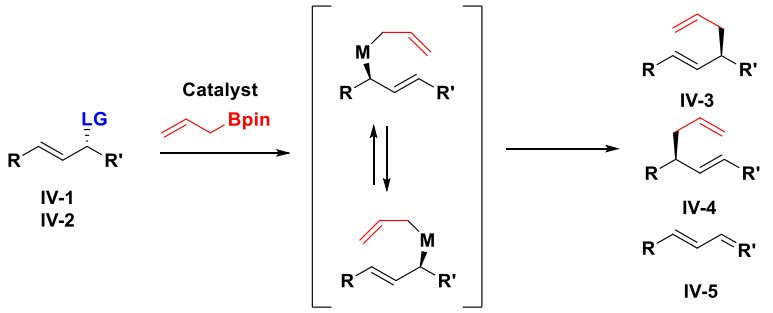
Scheme 4-12: Stereospecific allyl-allyl cross-coupling.

4.2. Stereospecific Synthesis of 1,5-Dienes Through an Allyl-Allyl Cross-Coupling Strategy.

4.2.1. Introduction and Objectives.

At the beginning of this project, there was only two examples of stereospecific allyl-allyl cross-coupling reactions.[21,22] We thought that a strategy involving the stereospecific synthesis of 1,5-dienes from enantiomerically enriched internal allylic compounds would be desirable. We got inspired by Morken's work and we decided to use palladium as our catalyst. However, Morken's work showed us that this reaction could have many problems. We envisioned that choosing the appropriate ligand should be critical for the transformation we wanted to perform. But not only the choice of the ligand in this transformation is crucial. We have learnt that the correct choice of the leaving group is also important for cross-coupling reactions. The objectives of this chapter include:

- Choose the appropriate catalytic system and leaving group to control the regioselectivity and stereospecificity of the reaction.
- Find the optimal condition to minimize the amount of β-hydride elimination product formed.
- Functionalize selectively both different double bonds in the 1,5-diene.



Scheme 4-13: Objectives of this chapter.

4.2.2. Synthesis of Starting Materials.

To study the proposed transformation, we prepared a series of allylic carbonates **IV-1** and ammonium salts **IV-2** (**Figure *4-2*** and **Figure *4-3***), following different procedures described below.

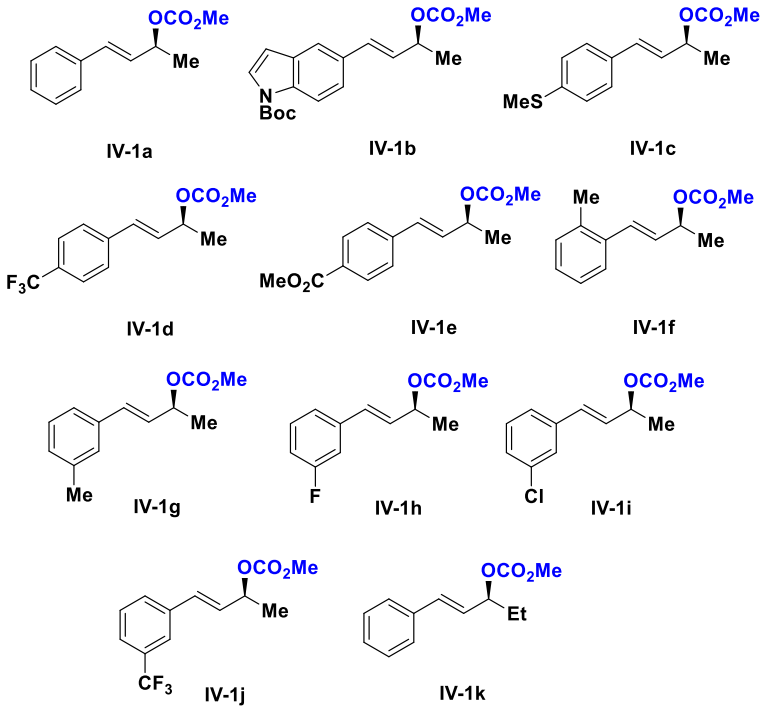


Figure 4-2: Enantiomerically enriched allylic carbonates.

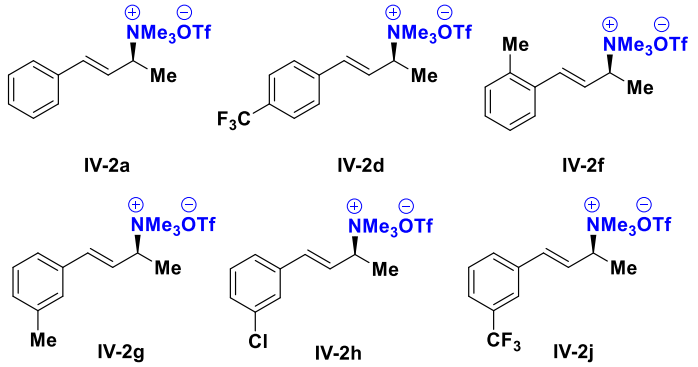
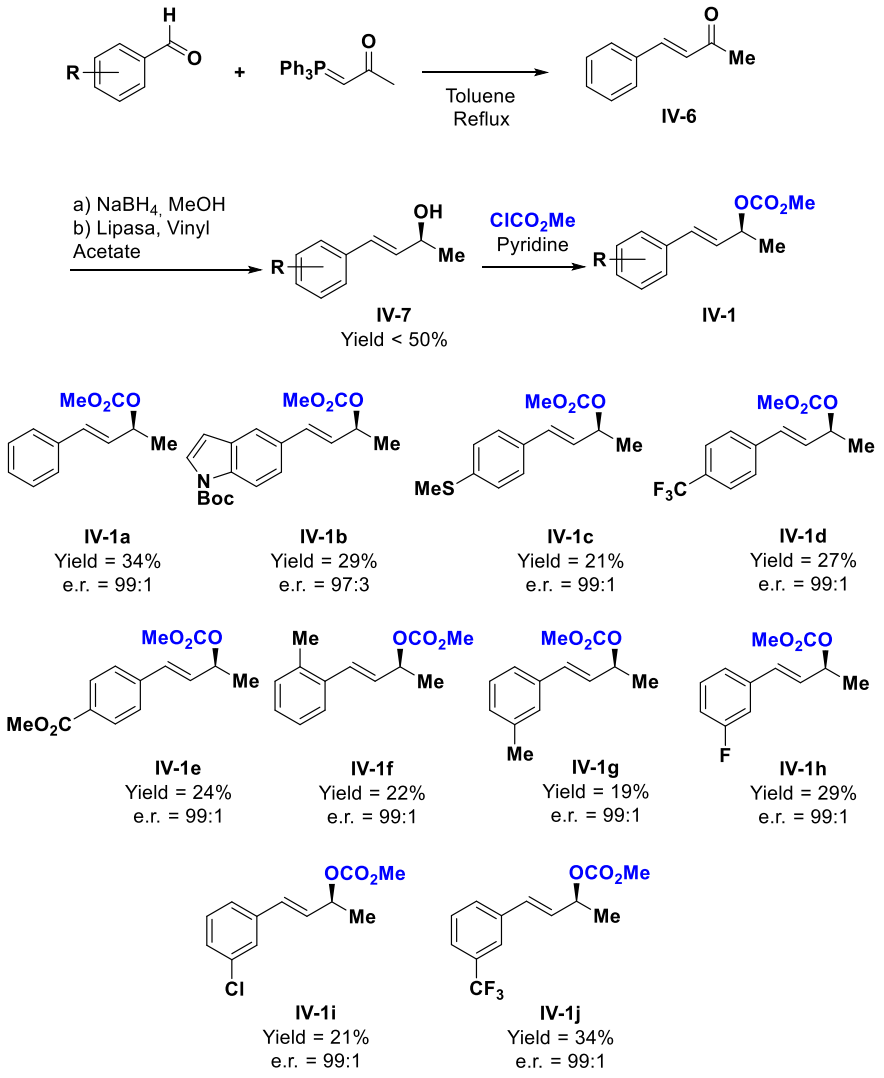


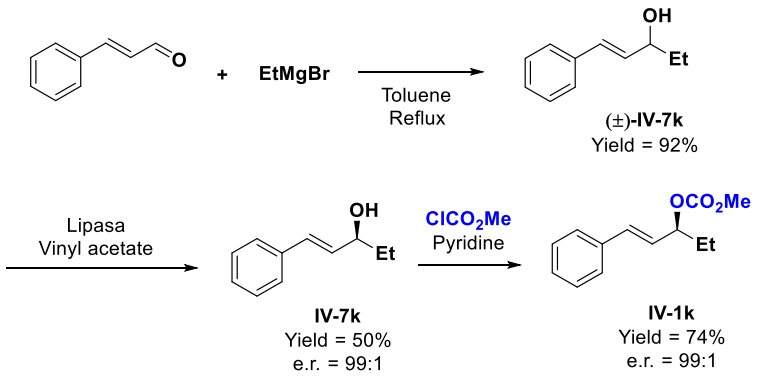
Figure 4-3: Enantiomerically enriched allylic ammonium salts.

The synthetic sequence to prepare allylic carbonates **IV-1a-j** started with the synthesis of the corresponding α-β unsaturated ketones **IV-6** by a Wittig reaction, to obtain the *E*-alkenes selectively. Then, 1,2-reduction of the corresponding α-β unsaturated ketones **IV-6**, afford racemic alcohols **(±)-IV-7**. Then, a kinetic resolution using Amano lipase from Pseudomones Fluorescens, provided enantiomerically enriched alcohols **IV-7**. Finally, carbonates **IV-1** were prepared by treatment of the alcohols with methyl chloroformiate (**Scheme *4-14***). The yields showed in the scheme are global yields. It is important to note that the maximum yield in the kinetic resolution is 50%.



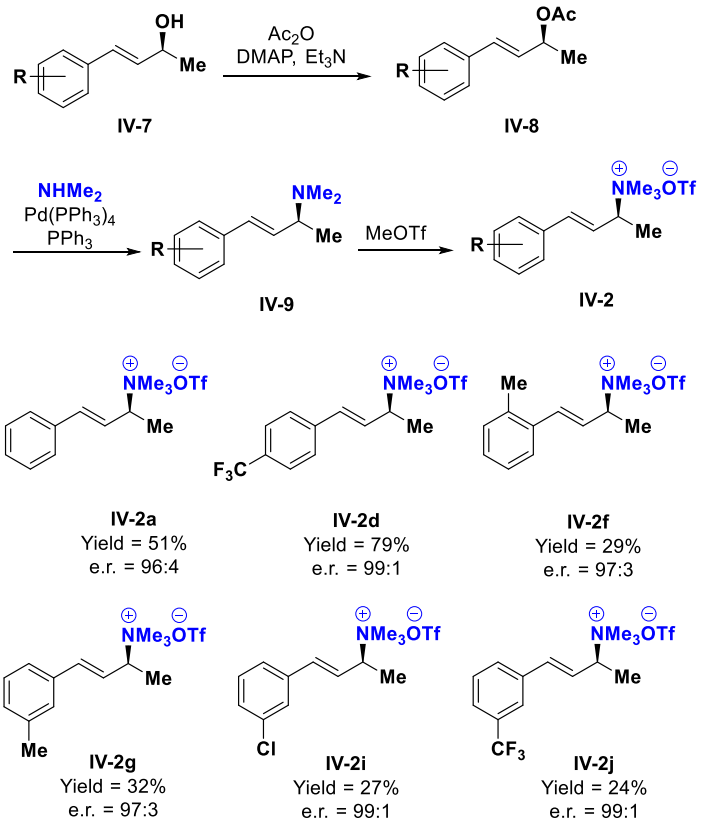
Scheme 4-14: Synthesis of allylic carbonates **IV-1a-j.**

Racemic alcohol **(±)-IV-7k** was prepared by addition of ethyl magnesium bromide to cinnamaldehyde. From here, kinetic resolution followed by treatment of the alcohol with methyl chloroformate afforded enantiomerically enriched allylic carbonate **IV-1k** (**Scheme *4-15***).



Scheme 4-15: Synthesis of **IV-1k**.

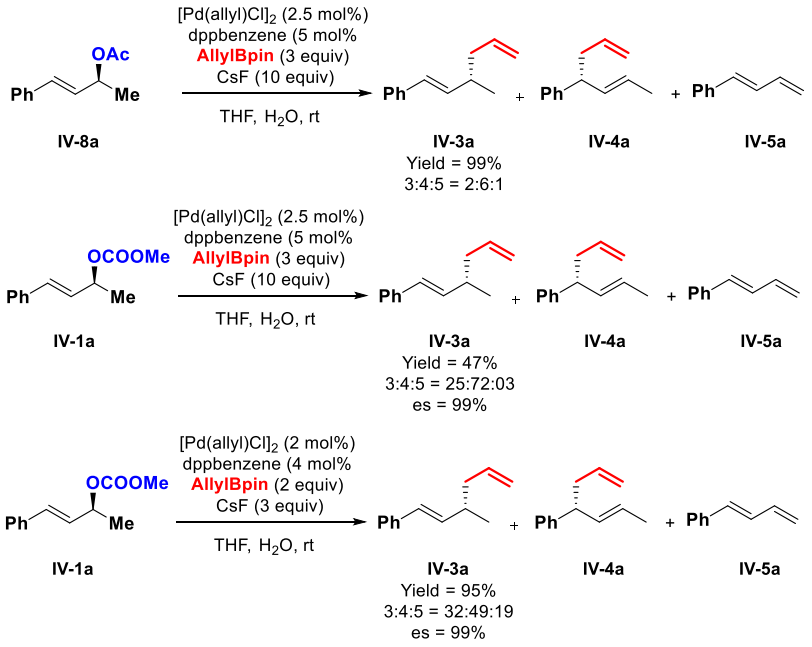
Allylic ammonium salts **IV-2** were synthesized from enantiomerically enriched allylic alcohols **IV-7**. Acetylation, followed by a stereospecific palladium catalyzed Tsuji-Trost reaction, provided dimethylamines **IV-9**. Finally, allylic ammonium salts **IV-2** were obtained upon treatment of amines **IV-9** with methyl triflate (**Scheme *4-16***). The yields showed in the scheme are global yields.



Scheme 4-16: Synthesis of allylic ammonium salts **IV-2**.

4.2.3. Palladium-Catalyzed Allyl-Allyl Cross-Coupling of Allylic Carbonates. Screening of Conditions.

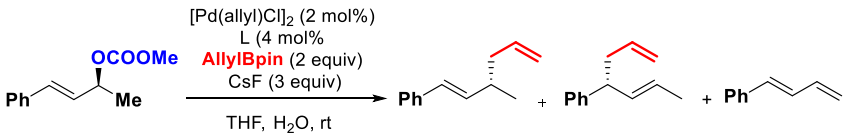
Motivated by the possibilities of this reaction, we tried the previously reported conditions by Morken (**Scheme *4-17***, top), using allylic carbonates instead of acetates. As catalyst, we used $[Pd(allyl)Cl]_2$ and dppbenzene as ligand. We obtained the desired product in 47%, but as a mixture of the three possible products. The stereospecificity of the reaction was great, but we did not achieve good regioselectivity and we found β-hydride elimination product in low amount (**Scheme *4-17***, mid). Decreasing the amount of cesium fluoride to 3 equivalents and the amount of allylBpin to 2 equivalents improve the yield of the reaction to 95%, but the regioselectivity was still unsatisfactory and the amount of β-hydride elimination product increase (**Scheme *4-17***, bottom), so we decided to look for the optimal conditions for this cross-coupling reaction.



Scheme 4-17: Palladium-catalyzed allyl-allyl cross-coupling of allylic carbonates.

We started our screening by changing the ligand to dppf, and surprisingly only **IV-3a** was obtained, but with a considerable amount of β-hydride elimination product **IV-5a** and in 32% yield (**Table *4-1***, entry 2). Using dppp or dppe did not improve the results of the reaction (**Table *4-1***, entries 3 and 4), but it is important to note that only regiosiomer **IV-3a** was observed. Triphenylphosphine gave similar results (**Table *4-1***, entry 5) and tri-*tert*-butylphosphine, a very bulky and electron-rich phosphine gave **IV-3a** in only 30% yield but no diene **IV-5a** was detected (**Table *4-1***, entry 6). It was CataCXium ABn, another bulky and electron-rich phosphine with two adamantly and one benzyl substituents, the one that gave the best result in this reaction. We obtained the desired product **IV-3a** with 87% isolated yield, excellent stereospecificity and only 8% of β-hydride elimination product was detected (**Table *4-1***, entry 7). Finally, using Johnphos as ligand did not achieve any conversion and we recover the starting material (**Table *4-1***, entry 9). We did not observe any conversion in the absence of cesium fluoride (**Table *4-1***, entry 10), ligand (**Table *4-1***, entry 11) or catalyst (**Table *4-1***, entry 12).

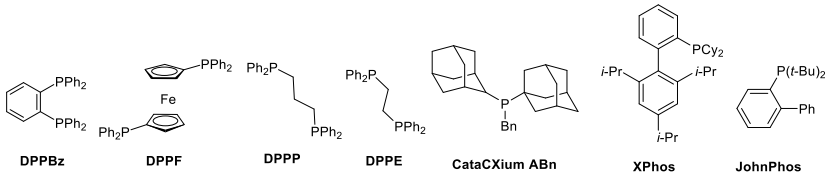
Table 4-1: Influence of the ligand.



IV-1a **IV-3a** **IV-4a** **IV-5a**

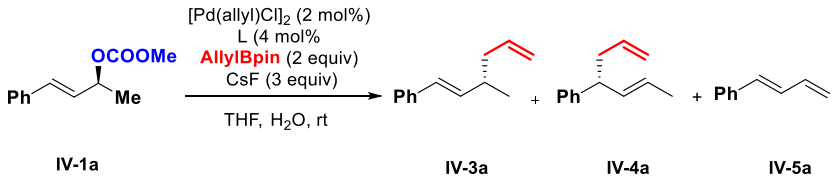
Entry	L (4 mol%)	Yield[a]	Ratio 3:4:5[a]	es (%)[c]
1	DPPBz	32	32:49:19	99%
2	DPPF	42	69:00:31	99%
3	DPPP	13	34:00:66	99%
4	DPPE	25	54:00:46	99%
5	PPh_3	21	58:00:42	99%
6	P(*t*-Bu)$_3$	30	100:00:00	99%
7	**CataCXiumABn**	**87[b]**	**92:00:08**	**99%**
8	Xphos	29	55:00:45	99%
9	JohnPhos	0	-	0
10[d]	CataCXiumABn	0	-	0
11[e]	-	0	-	0
12[f]	CataCXiumABn	0	-	0

Reaction conditions: **IV-1a** (0.2 mmol, 1.0 equiv), AllylBpin (2.0 equiv), $[Pd(allyl)Cl]_2$ (2 mol%), Ligand (4 mol%), CsF (3.0 equiv), H_2O (15.0 equiv), THF (0.14 M), rt, 16h, unless otherwise noted. [a]Yield and ratio of the product determined by ^{1}H-NMR using quinoline as internal standard. Yields corrected based on of the amount of diene formed. [b]Isolated yield after column chromatography. [c]Determined by chiral GC-MS. [d]No base was used. [e]No ligand was used. [f]No palladium was used.



With the optimal conditions in hand, we briefly studied the influence of the leaving group in the transformation. We were glad to see that trimethyl ammonium salts gave also excellent results in the allyl-allyl cross-coupling and yielded the desired product with 82% yield and perfect stereospecificity (**Table *4-2***, entry 2). Surprisingly, the corresponding allylic acetate previously used by Morken, afforded **IV-3a** in only 9% yield and with complete loss of the chirality transfer (**Table *4-2***, entry 3). A primary allylic amine and the dimethyl amine derivative, previously used as electrophiles in Tsuji-Trost type reactions,[23] did not react under the optimized conditions (**Table *4-2***, entries 4 and 5).

Table 4-2: Influence of the leaving group.

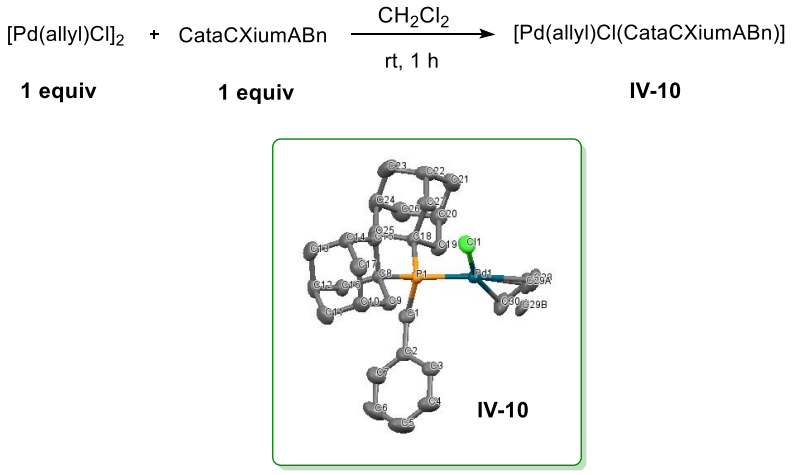


Entry	Leaving Group	Yield (3:4:5)[a], [b]	es (%)[c]
1	**OCO_2Me**	**87 (92:00:08)[d]**	**99%**
2	**NMe_3OTf**	**82 (94:00:6)[d]**	**99%**
3	OAc	9 (90:00:10)	0%
4	NH_2	0	0
5	NMe_2	0	0

Reaction conditions: **Allylic compound** (0.2 mmol, 1.0 equiv), AllylBpin (2.0 equiv), $[Pd(allyl)Cl]_2$ (2 mol%), CataCXium ABn (4 mol%), CsF (3.0 equiv), H_2O (15.0 equiv), THF (0.14 M), rt, 16h, unless otherwise noted. [a]Isolated yield after column chromatography. [b]Ratio of the product determined by ^{1}H-NMR using quinoline as internal standard. [c]Determined by chiral GC-MS. [d]Yields corrected based on the amount of diene formed.

[23] Li, M. B.; Wang, Y.; Tian, S. K. *Angew. Chem. Int. Ed.* **2012**, *51*, 2968-2971.

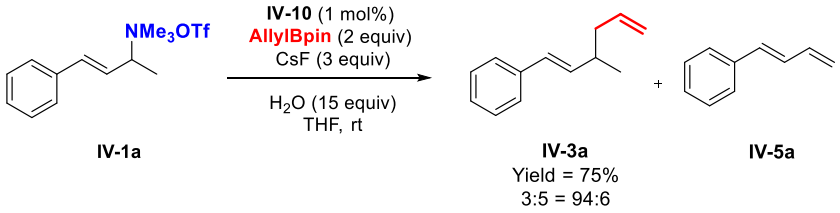
To gain insight into the Pd(II) precatalyst involved in the reaction we mixed one equivalent of $[Pd(allyl)Cl]_2$ and two equivalents of cataCXium ABn to obtain **IV-10** as a white solid. This solid was recrystallized from dichloromethane to provide suitable crystals for X-ray diffraction (**Scheme *4-18***).[24]



Scheme 4-18: Synthesis and characterization of **IV-10**.

When we used 1 mol% of the preformed catalyst **IV-10** under the optimized conditions, diene **IV-3a** was obtained in 75% yield, as a single regioisomer and with excellent stereospecificity. Along the desired product, we obtained 6% of diene (**Scheme *4-19***).

[24] CCDC 1953214 contains the supplementary crystallographic data. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html



Scheme 4-19: Model reaction using the preformed Pd(II) catalyst.

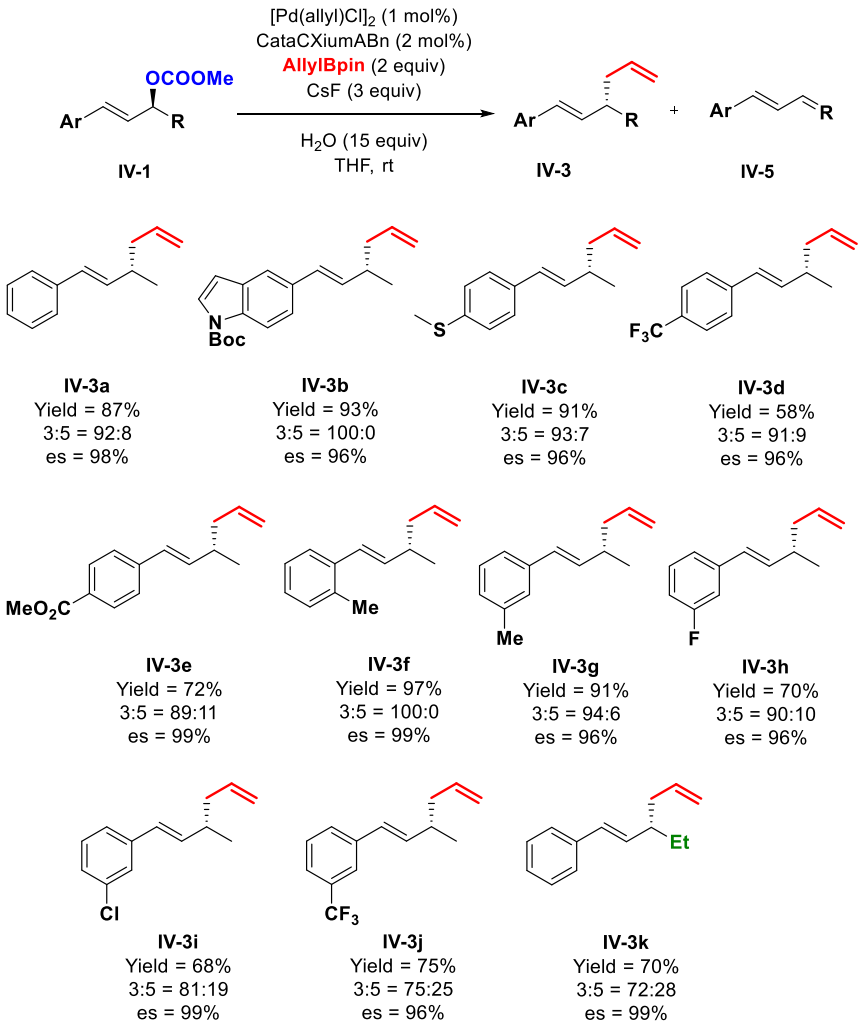
4.2.4. Scope of the Reaction.

With the optimal conditions in hand, we next tested the enantiomerically enriched allylic carbonates prepared previously (**Figure *4-2***) to determine the structural scope of the reaction (**Scheme *4-20***). Enantiomeric ratios were determined by chiral GC-MS. The ratios between the product and the undesired diene were measured by ^{1}H-NMR. We were not able to separate them by silica chromatography but it was possible to get rid of the diene by a simple Diels-Alder reaction with maleic anhydride.[22] Yields were corrected based on the amount of diene in the mixture.

Electron-donating groups in the para-position worked really good under the optimal conditions. Using carbonate **IV-1b**, with a Boc-protected indol, gave the product **IV-3b** with no trace of the β-hydride elimination product. Sulfur atoms were also compatible with the reaction conditions, obtaining product **IV-3c** with 91% yield and only 7% of diene. Trifluoromethyl substituent at the *para* position, as starting material gave the desired coupled product **IV-3d** with 58% yield and only 9% of diene. Esters were compatible with the reaction conditions and **IV-1e** gave the desired product **IV-3e** in good yield and only 11% of diene. Methyl substituents were compatible in both the *orto* and *meta* position. The results using **IV-1f** as starting material was especially good, and it gave **IV-3f** with 97% yield without any appreciable amount of diene.

Fluorine and chlorine substituted allylic carbonates **IV-1h** and **IV-1i** yielded the desired products with good results, however the amount of diene was higher in the case of **IV-3i**, going up to 19% (with a chlorine substituent). The result when we used **IV-1j**, with the trifluoromethyl group at the *meta* position was similar to that of **IV-3i** and the amount of diene went up to 25%. Finally, changing the methyl substituent in the allylic position with an ethyl moiety (**IV-1k**) increased the amount of diene to 28%.

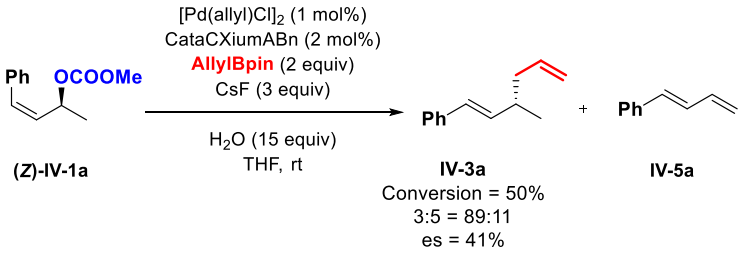
It is important to highlight that in all cases the enantiomeric information was preserved almost completely. In addition, no trace of the other regioisomer was detected in any of the product.



Scheme 4-20: Scope of the stereospecific allyl-allyl cross-coupling reaction.

We also tried the reaction using the *Z*-allylic compound **(*Z*)-IV-1a** and we obtained **IV-3a** with 50% conversion but only 41% of stereospecificity. This result could indicate that a π-allyl palladium complex is indeed formed. The loss of enantiomeric information could be due to the attack of

Pd(0) to the π-allyl complex. The results showed in **Scheme *4-21*** are the average of three experiments.



Scheme 4-21: Allyl-allyl cross-coupling reaction using *Z*-allylic carbonate.

4.2.5. Palladium-Catalyzed Allyl-Allyl Cross-Coupling of Allylic Ammonium Salts. Scope of the Reaction.

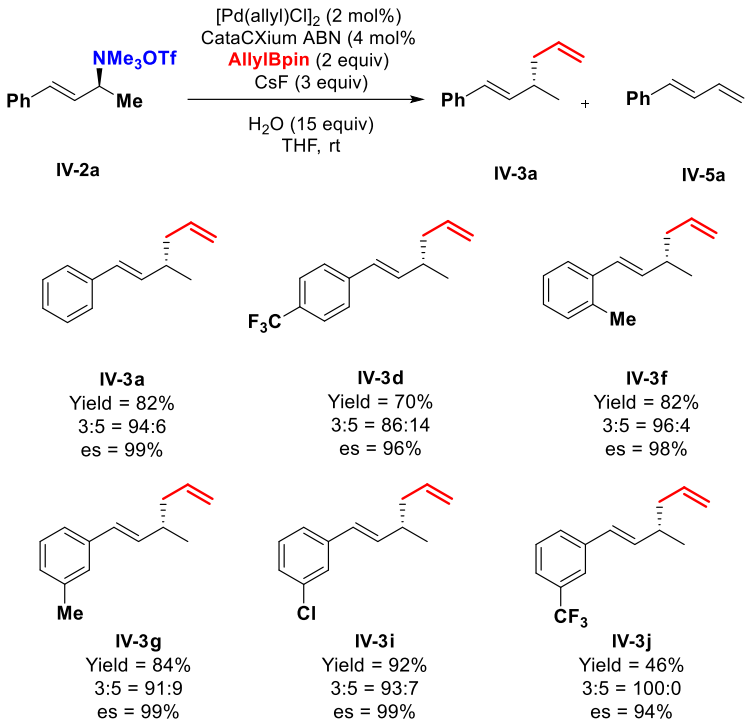
As described in **Table *4-2***, allylic ammonium salt **IV-2a** underwent the Pd catalyzed allyl-allyl cross coupling with similar efficiency to that shown for the carbonate derivative. This result prompted us to briefly investigate if this was a general trend and to compare the reactivity between allylic acetates, carbonates and ammonium salts in this transformation (**Table *4-2***).

With the optimal conditions in hand, we tested the enantiomerically enriched allylic ammonium salts prepared previously (**Figure *4-3***) to determine the structural scope of the reaction (**Scheme *4-22***). Enantiomeric ratios were determined by chiral GC-MS. The ratios between the product and the undesired diene were measured by ^{1}H-NMR. We were not able to separate them by silica chromatography but it was possible to get rid of the diene by a simple Diels-Alder reaction with maleic anhydride.[22] Yields were corrected based on the amount of diene in the mixture.

Using ammonium salt **IV-2d**, with a trifluoromethyl substituent at the *para* position, as starting material yielded the desired 1,5 diene **IV-3d** with good yield and 14% of diene. Methyl substituents are compatible in both the *orto* and *meta* position. Again, the results using **IV-2f** as starting material was better, and it gave **IV-3f** with 82% yield with only 4% of diene.

Chlorine substituted allylic ammonium salt **IV-2i** yielded the desired product **IV-3i** with good results. However, when we used **IV-2j**, with the trifluoromethyl group at the *meta* position, the yield decreased, but we did not observe any formation of the β-hydride elimination product.

It is important to highlight that in all cases the enantiomeric information was preserved almost completely. In addition, no trace of the other possible regioisomer was detected in any of the products.

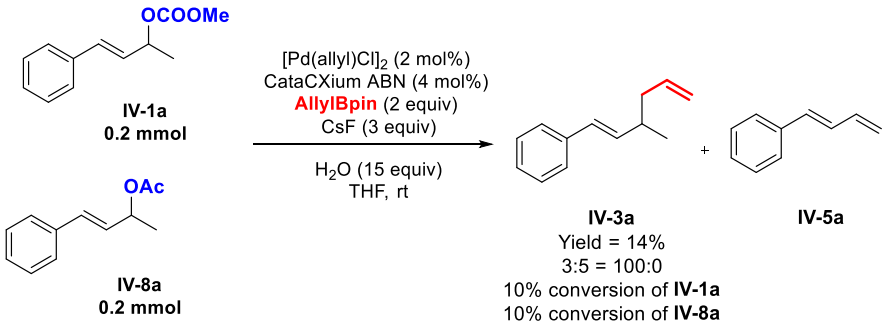


Scheme 4-22: Scope of the stereospecific allyl-allyl cross-coupling reaction using allylic ammonium salts.

4.2.6. Competition Experiments.

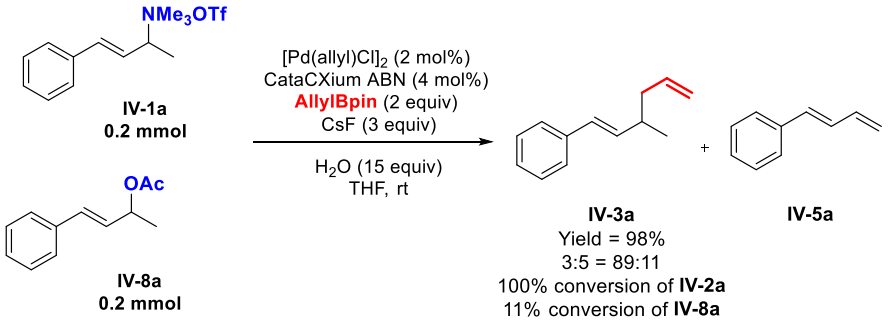
To test the different reactivity between allylic carbonates and ammonium salts we did a series of competition experiments. First, we tested the reactivity of the carbonate **IV-3a** against allylic acetate **IV-8a** (**Scheme *4-23***). We put 0.2 mmol of each compound (**IV-1a** and **IV-8a**) under the reaction conditions. Surprisingly, we observed that only 10% of the starting

carbonate **IV-1a** was converted. In the case of the acetate, we also observed 10% of conversion.



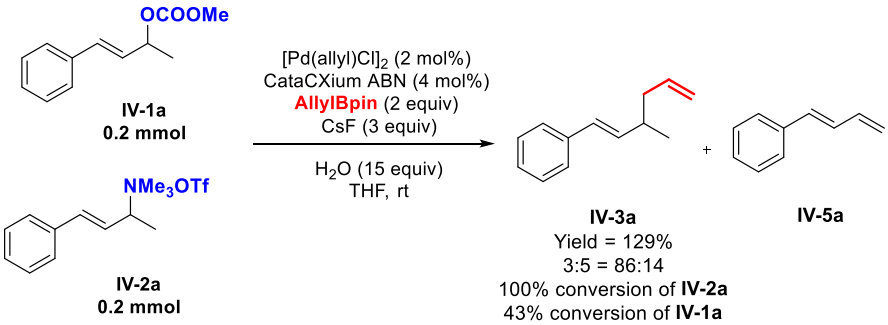
Scheme 4-23: Competition experiment between allylic carbonates and acetates.

We next tested the reactivity of the ammonium salt **IV-2a** against allylic acetate **IV-8a** using the same procedure (**Scheme *4-24***). In this case, we observed total conversion of the ammonium salt and only 11% conversion of the acetate.



Scheme 4-24: Competition experiment between allylic ammonium salts and acetates.

Finally, we tested differences between both compounds (**Scheme *4-25***). We put 0.2 mmol of each compound (**IV-1a** and **IV-2a**) under the reaction conditions. We observed total conversion of the ammonium salt **IV-2a** and 43% conversion of **IV-1a**.



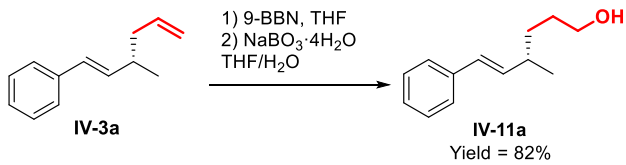
Scheme 4-25: Competition experiment between allylic carbonates and ammonium salts.

These results could mean that ammonium salts are more reactive than the corresponding carbonates under the reaction conditions. Also, it seemed as the acetates would shut down the catalytic system when they reacted.

4.2.7. Selective functionalization of the alkenes in the 1,5-dienes.

Tu further demonstrate the utility of the synthetized 1,5-dienes we designed a series of transformations, in order to take advantage of the different stereoelectronic properties of both alkenes.

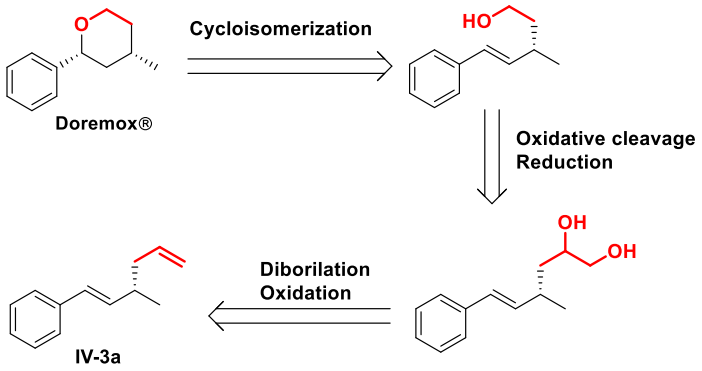
We started trying to functionalize the terminal olefin. Our first attempts using OsO_4 and α-AD-mix gave us complex mixtures of products. We found out that treating **IV-3a** with 9-BBN as borylating agent and subsequent oxidation with sodium perborate gave us the terminal alcohol **IV-11a** (**Scheme *4-26***).



Scheme 4-26: Selective hydroboration/oxidation of compound **IV-3a**.

Next, we planned to transform **IV-3a** into the rose oxide derivative **Doremox®**.[25] This derivative was first reported in 1993 by Firmenich, and it increased the substantivity of rose scent in the skin. We envisioned that **Doremox®** could be obtained by a simple cycloisomerization from the alcohol (**Scheme *4-27***, first step). This alcohol could be obtained from the corresponding diol coming from diborylate **IV-3a** (**Scheme *4-27***).

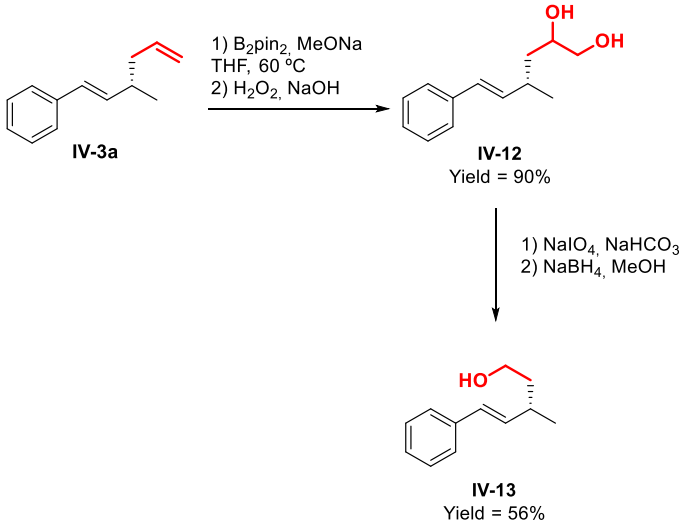
[25] a) Brenna, E.; Fuganti, C.; Ronzani, S.; Serra, S. *Can. J. Chem.* **2002**, *80*, 714-723. b) Coulombel, L.; Weiwer, M.; Duñach, E. *Eur. J. Org. Chem.* **2009**, 5788-5795.



Scheme 4-27: Retrosynthetic analysis of **Doremox®**.

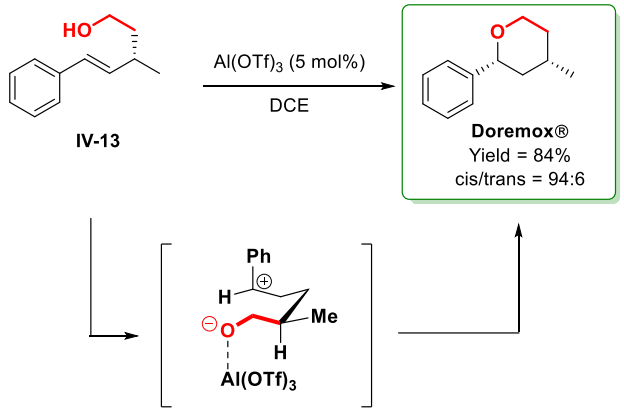
We decided to attempt the synthesis of this compound. We started the synthesis by a metal-free diborylation reaction in the terminal olefin,[26] followed by oxidation of the resulting crude mixture to obtain a diastereomeric mixture of diol **IV-12** with excellent yield. We continued the synthesis by the oxidative cleavage of the diol with $NaIO_4$, followed by reduction of the formed aldehyde to obtain alcohol **IV-13** (**Scheme *4-28***).

[26] Bonet, A.; Pubill-Ulldemolins, C.; Bo, C.; Gulyas, H.; Fernandez, E. *Angew. Chem. Int. Ed.* **2011**, *50*, 7158-7161.



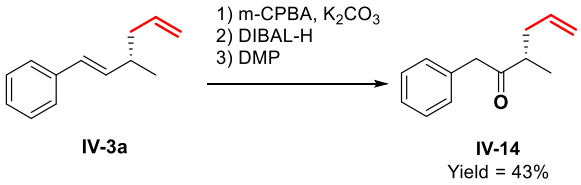
Scheme 4-28: Synthesis of alcohol **IV-13**.

Finally, by an $Al(OTf)_3$ catalyzed cycloisomerization, we obtained the desired product with excellent yield and a diastereomeric ratio of 94:6 (**Scheme *4-29***).



Scheme 4-29: Synthesis of the rose oxide derivative Doremox®.

To functionalize the internal olefin, we selected an epoxidation using *m*-CPBA, obtaining a diastereomeric mixture of epoxides. Then, regioselective opening of the epoxide by treatment with DIBAL-H, followed by oxidation with Dess-Martin periodinane afforded ketone **IV-14** with a global yield of 43% (**Scheme *4-30***).



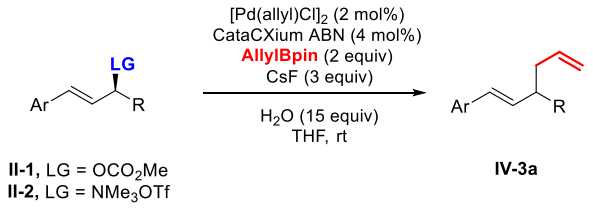
Scheme 4-30: Synthesis of ketone **IV-14**.

4.3. Conclusions.

In this chapter we have described the regioselective and stereospecific palladium-catalyzed allyl-allyl cross-coupling between allylic carbonates or ammonium salts and allyl boronates leading to the corresponding 1,5-dienes. We have solved some of the remnant problems in this kind of reactions as the regioselectivity and the stereospecificity. Also, we have minimized the amount of b-hydride elimination product formed in the reaction (**Scheme *4-31***).

The nature of the leaving group and the ligand used in the reaction are key factors to control the regioselectivity and the stereospecificity of the reaction. The use of carbonates or ammonium salts along an electron rich and bulky monodentate ligand was crucial to control the outcome of the reaction.

Furthermore, taking advantage of the two different olefins formed in the reaction, we have selectively functionalized both of them to access valuable compounds as the cyclic ether Doremox®.



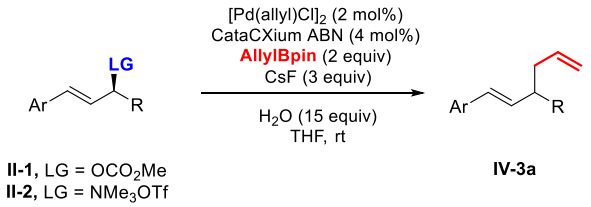
Scheme 4-31: Palladium-catalyzed allyl-allyl cross-coupling between allylic carbonates or ammonium salts and allylic boronates.

4.4. Conclusions.

En este capítulo, se ha descrito el acoplamiento cruzado alilo-alilo entre carbonatos alílicos o sales de amonio alílicas y boronatos alílicos para la síntesis de 1,5-dienos de manera regioselectiva y estereoespecífica. Con esta metodología, hemos solventado los problemas de regioselectividad y estereoespecificidad que acarrean este tipo de reacciones. También, hemos conseguido minimizar la cantidad de producto de β-eliminación de hidruro formado durante la reacción (**Esquema *4-32***).

La naturaleza del grupo saliente y del ligando son factores importantes para el control de la regioselectividad y la estereoespecificidad. El uso de carbonatos alílicos o sales de amonio alílicas junto a un ligando rico, con gran impedimento estérico y monodentado fue crucial para controlar el resultado de la reacción.

Además, aprovechando que durante la reacción se forman dos olefinas con diferentes propiedades estéricas y electrónicas, hemos funcionalizado selectivamente ambos dobles enlaces llegando a productos de gran valor, como el éter cíclico Doremox®.



Esquema 4-32: Acoplamiento cruzado alilo-alilo catalizado por paladio entre carbonatos alílicos o sales de amonio alílicas y boronatos alílicos.

4.5. Supplementary Data.

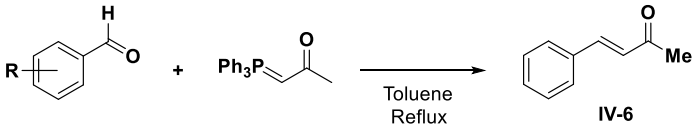
Tetrahydrofuran and dichloromethane were purified by passing through a Pure Solv™ column drying system from Innovative Technology, Inc. Additionally, Tetrahydrofuran and dichloromethane were degassed passing Argon through them for 15 min. Diethyl ether was dried using activated 4Å molecular sieves and stored under argon. Unless indicated otherwise, all reactions were conducted under an argon atmosphere using flame-dried glassware with standard vacuum-line techniques. NMR spectra were acquired on a Bruker 300 spectrometer, running at 300, and 75 MHz for ^{1}H and ^{13}C NMR respectively. Chemical shifts (δ) are reported in ppm relative to residual solvent signals ($CDCl_3$, 7.26 ppm for ^{1}H NMR and 77.2 ppm for ^{13}C NMR respectively). ^{13}C NMR spectra were acquired on a broad band decoupled mode. The following abbreviations are used to describe peak patterns when appropriate: s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), sex (sextet), hept (septuplet), m (multiplet), br (broad). Analytical thin layer chromatography (TLC) was performed using pre-coated aluminum-backed plates (Merck Kieselgel 60 F254) and visualized by ultraviolet irradiation or phosphomolybdic acid dip or potassium permanganate dip. Purification of reaction mixtures was carried out by flash chromatography (FC) using silica gel Merck-60. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. The enantiomeric ratio (e.r.) of the products was determined by stationary phase SFC, HPLC or GC-MS using chiral columns. Mass Spectrometry (MS) and High Resolution Mass Spectrometry (HRMS) were registered in a spectrometer GCT Agilent Technologies 6890N using Electronic Impact (E.I.) techniques at 70 eV, Fast Atom Bombardment and electrospray (ESI^+ or ESI^-).

All ligands, metal complexes, allylboronic acid pinacol ester and Amano Lipase from Pseudomonas fluorescens were acquired from commercial

sources and were used without further purification. Cinnamyl alcohol, 4-Phenyl-3-buten-2-one were purchased from Sigma Aldrich and were used without purification.

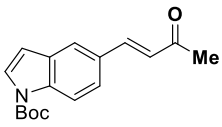
4.5.1. Synthesis of starting materials.

4.5.1.1. *Synthesis of α,β-unsaturated ketones* **IV-6.**



To an oven-dried round bottom flask was added the corresponding aromatic aldehyde (1.0 equiv), 1-(triphenylphosphoranylidene)-2-propanone (1.2 equiv) and toluene (2 mL/mmol of aldehyde). The reaction mixture was stirred for 16 h at reflux. Silica gel was added to the mixture and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography using the appropriate mixture of solvents.

tert-Butyl (*E*)-5-(3-oxobut-1-en-1-yl)-1H-indole-1-carboxylate, **IV-6b**.



IV-6b

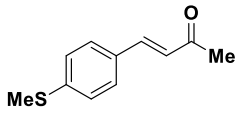
From *tert*-butyl 5-formyl-1H-indole-1-carboxylate (8.5 g, 34.7 mmol), following the general procedure described above, compound **IV-6b** (8.41 g, 29.5 mmol) was obtained in 85% yield as a yellow solid after flash column chromatography (Cy/EtOAc, 90/10).

^{1}H NMR, **^{13}C NMR** and **MS** data were consistent with literature values.[27] **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.17 (d, *J* = 8.6 Hz, 1H), 7.76-7.59

[27] Zhang, H.; Han, M.; Chen, T.; Xu, L.; Yu, L. *RSC Adv.* **2017**, *7*, 48214-48221.

(m, 4H), 6.76 (dd, *J* = 16.3, 1.9 Hz, 1H), 6.60 (s, 1H), 2.41 (s, 3H), 1.69 (s, 9H).

(*E*)-4-(4-(Methylthio)phenyl)but-3-en-2-one, **IV-6c**.

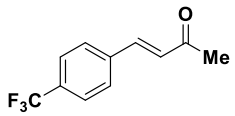


IV-6c

From 4-(methylthio)benzaldehyde (4.6 g, 30.0 mmol), following the general procedure described above, compound **IV-6c** (5.76 g, 30.0 mmol) was obtained in 99% yield as a white solid after flash column chromatography (Cy/EtOAc, 90/10).

^{1}H NMR, **^{13}C NMR** and **MS** data were consistent with literature values.[28] **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.46 (m, 3H), 7.26 – 7.19 (m, 2H), 6.67 (d, *J* = 16.3 Hz, 1H), 2.50 (s, 3H), 2.37 (s, 3H).

(*E*)-4-(4-(Trifluoromethyl)phenyl)but-3-en-2-one, **IV-6d**.



IV-6d

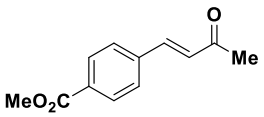
From 4-(trifluoromethyl)benzaldehyde (7.80 g, 45.0 mmol), following the general procedure described above, compound **IV-6d** (9.78 g, 45.0 mmol) was obtained in 99% yield as a yellow solid after flash column chromatography (Cy/EtOAc, 90/10).

^{1}H NMR, **^{13}C NMR** and **MS** data were consistent with literature values.[29] **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.65 (s, 4H), 7.52 (d, *J* = 16.3 Hz, 1H), 6.77 (d, *J* = 16.3 Hz, 1H), 2.40 (s, 3H).

[28] Antiñolo, A.; Carrillo-Hermosilla, F.; Cadierno, V.; Garcia-Alvarez, J.; Otero, A. *ChemCatChem* **2012**, *4*, 123-128.

[29] Zhang, S.-L.; Deng, Z.-Q. *Org. Biomol. Chem.* **2016**, *14*, 7282-7294.

Methyl (*E*)-4-(3-oxobut-1-en-1-yl)benzoate, **IV-6e**.

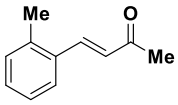


IV-6e

From methyl 4-formylbenzoate (4.9 g, 30.0 mmol), following the general procedure described above, compound **IV-6e** (5.49 g, 27.0 mmol) was obtained in 90% yield as a white solid after flash column chromatography (Cy/EtOAc, 90/10).

^{1}H NMR, **^{13}C NMR** and **MS** data were consistent with literature values.[29] **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.06 (d, *J* = 8.4 Hz, 2H), 7.60 (d, *J* = 8.3 Hz, 2H), 7.52 (d, *J* = 16.3 Hz, 1H), 6.78 (d, *J* = 16.3 Hz, 1H), 3.93 (s, 3H), 2.40 (s, 3H).

(*E*)-4-(*o*-Tolyl)but-3-en-2-one, **IV-6f**.

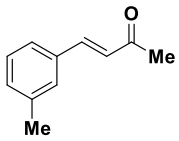


IV-6f

From 2-methylbenzaldehyde (2.4 g, 20.0 mmol), following the general procedure described above, compound **IV-6f** (2.69 g, 16.8 mmol) was obtained in 84% yield as a yellow oil after flash column chromatography (Cy/EtOAc, 90/10).

^{1}H NMR, **^{13}C NMR** and **MS** data were consistent with literature values.[29] **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.83 (d, *J* = 16.1 Hz), 7.57 (d, *J* = 7.2 Hz, 1H), 7.32-7.20 (m, 3H), 6.66 (d, *J* = 16.0 Hz, 1H), 2.46 (s, 3H), 2.39 (s, 3H).

(*E*)-4-(*m*-Tolyl)but-3-en-2-one, **IV-6g**.

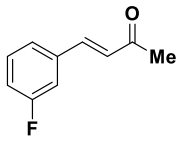


IV-6g

From 3-methylbenzaldehyde (2.4 g, 20.0 mmol), following the general procedure described above, compound **IV-6g** (2.98 g, 18.6 mmol) was obtained in 93% yield as a yellow oil after flash column chromatography (Cy/EtOAc, 90/10).

^{1}H NMR, **^{13}C NMR** and **MS** data were consistent with literature values.[30] **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.50 (d, *J* = 16.3 Hz, 1H), 7.40 – 7.19 (m, 4H), 6.72 (d, *J* = 16.3 Hz, 1H), 2.39 (s, 6H).

(*E*)-4-(3-Fluorophenyl)but-3-en-2-one, **IV-6h**.

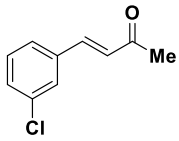


IV-6h

From 3-fluorobenzaldehyde (3.7 g, 30.0 mmol), following the general procedure described above, compound **IV-6h** (4.72 g, 28.8 mmol) was obtained in 96% yield as a yellow oil after flash column chromatography (Cy/EtOAc, 90/10).

^{1}H NMR, **^{13}C NMR** and **MS** data were consistent with literature values.[31] **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.48 (d, *J* = 16.3 Hz, 1H), 7.36 (m, 2H), 7.26 (m, 1H), 7.12 (m, 1H), 6.72 (d, *J* = 16.3 Hz, 1H), 2.40 (s, 3H).

(*E*)-4-(3-Chlorophenyl)but-3-en-2-one, **IV-6i**.

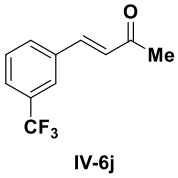


IV-6i

From 3-chlorobenzaldehyde (2.8 g, 20.0 mmol), following the general procedure described above, compound **IV-6i** (3.40 g, 18.8 mmol) was obtained in 94% yield as a yellow oil after flash column chromatography (Cy/EtOAc, 90/10).

^{1}H NMR, **^{13}C NMR** and **MS** data were consistent with literature values.[30] **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.52–7.30 (m, 5H), 6.71 (d, *J* = 15.8 Hz, 1H), 2.38 (s, 3H).

(*E*)-4-(3-(Trifluoromethyl)phenyl)but-3-en-2-one, **IV-6j**.

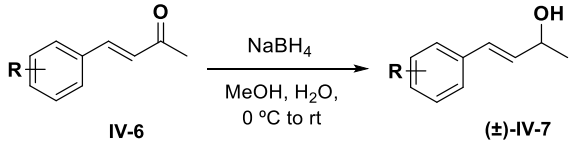


IV-6j

From 3-(trifluoromethyl)benzaldehyde (5.0 g, 28.7 mmol), following the general procedure described above, compound **IV-6j** (5.71 g, 26.7 mmol) was obtained in 93% yield as a yellow solid after flash column chromatography (Cy/EtOAc, 90/10).

^{1}H NMR, **^{13}C NMR** and **MS** data were consistent with literature values.[31] **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.79 (s, 1H), 7.72 (d, *J* = 8.0 Hz, 1H), 7.62 (d, *J* = 8.0 Hz, 1H), 7.56-7.50 (m, 2H), 6.78 (d, *J* = 16.0 Hz, 1H), 2.40 (s, 3H).

4.5.1.2. *Synthesis of allylic alcohols*, **IV-7**.



IV-6 **(±)-IV-7**

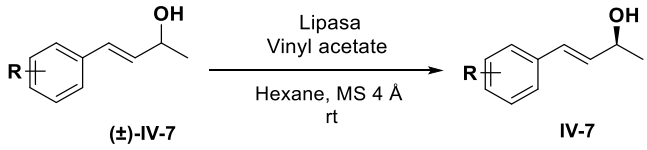
To an oven-dried round bottom flask was added the corresponding ketone (1 equiv) in methanol (0.3M) and cooled to 0 ºC. To this solution,

[30] Pan, G.-F.; Zhu, X.-Q.; Guo, R.-L.; Gao, Y.-R.; Wang, Y.-Q. *Adv. Synth. Catal.* **2018**, *360*, 4774-4783.

[31] Liu, J.; Zhu, X.-R.; Ren, J.; Chen, W.-D.; Zeng, B.-B. *Synlett*, **2013**, *24*, 2740-2742.

sodium borohydride (1.45 equiv) in H_2O was added dropwise and the reaction mixture was stirred for 1 h at 0 ºC. Then, the mixture was warmed to room temperature and stirred overnight. The reaction mixture was quenched with saturated aqueous solution of ammonium chloride and extracted with Et_2O (3x), dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography on silica gel using the appropriate mixture of solvents.

The enantiopure allylic alcohols were obtained by kinetic resolution using Amano Lipase from Pseudomonas fluorescens following the reported procedure.[32]

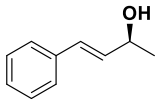


(±)-IV-7 **IV-7**

To an oven-dried round bottom flask was added the racemic alcohol **(±)-IV-7** (1 equiv), molecular sieves (50 % w/w) and Amano Lipase from Pseudomonas fluorescens (50 % w/w). The flask was connected to an argon-vacuum line, evacuated and backfilled with argon (x3). n-Hexane (150 mL) was added, followed by vinyl acetate (3 equiv) and the reaction mixture was stirred at room temperature for 24 h. After completion (checked by chiral SFC or HPLC) the reaction was filtered, and the solvent was removed under reduced pressure. The product is purified by flash column chromatography on silica gel using the appropriate mixture of solvents.

[32] Li, Z.; Parr, B. T.; Davies, H. M. L. *J. Am. Chem. Soc.* **2012**, *184*, 10942.

(–)-(*S*,*E*)-4-Phenylbut-3-en-2-ol, **IV-7a**.



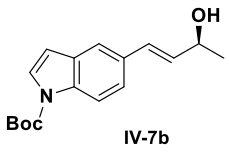
IV-7a

From (*E*)-4-phenylbut-3-en-2-one (5.0 g, 34.2 mmol), following the general procedure described above, compound **(±)-IV-7a** (4.7 g, 31.5 mmol) was obtained in 92% yield as a pale yellow oil after flash column chromatography (Cy/EtOAc, 90/10).

^{1}H NMR, **^{13}C NMR** and **MS** data were consistent with literature values.[33] **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 7.41-7.24 (m, 5H), 6.56 (d, *J* = 15.8 Hz, 1H), 6.27 (d, *J* = 15.8, 6.4 HZ, 1H), 4.51 (quint, *J* = 6.3 Hz, 1H), 1.92 (s broad, 1H), 1.38 (d, *J* = 6.5 Hz, 3H).

From **(±)-IV-7a** (4.0 g, 27 mmol), following the general procedure described above, compound **IV-7a** (1.6 g, 10.8 mmol) was obtained in 40% yield as a pale yellow oil after flash column chromatography (Cy/EtOAc, 90/10). Compound **IV-7a** was obtained in 99:1 enantiomeric ratio determined by HPLC using Chiralpak-IC column [Hexane/iPrOH (99:1)], 1.0 mL/min, τ_{major} = 11.8 min, τ_{minor} = 10.5 min. **$[\alpha]^{20}_D$** = –28.8 (*c* = 1.0, $CHCl_3$). We assigned the absolute configuration by comparison of the optical rotation with that of the previously reported compound.[33]

(–)-*tert*-Butyl-(*S*,*E*)-5-(3-hydroxybut-1-en-1-yl)-1H-indole-1-carboxylate, **IV-7b**.



IV-7b

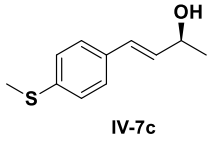
From *tert*-butyl (*E*)-5-(3-oxobut-1-en-1-yl)-1*H*-indole-1-carboxylate (9.88 g, 34.6 mmol), following the general procedure described above, compound **(±)-IV-7b** (32.9 mmol) was obtained in 95% yield as a pale yellow oil after flash column chromatography (Cy/EtOAc, 85/15).

[33] Inagaki, T.; Ito, A.; Ito, J.; Nishiyama, H. *Angew. Chem. Int. Ed.* **2010**, *49*, 9384-9387.

^{1}H-RMN (300 MHz, $CDCl_3$): δ 7.96 (d, *J* = 8.7 Hz, 1H), 7.45 (d, *J* = 3.6 Hz, 1H), 7.35 (s broad, 1H), 7.25 (d, *J* = 8.7 Hz, 1H), 6.52 (d, *J* = 16.2 Hz, 1H), 6.39 (d, *J* = 3.5 Hz, 1H), 6.11 (dd, *J* = 15.8, 6.4 Hz, 1H), 4.37 (quint, *J* = 6.4 Hz, 1H), 2.24 (s broad, 1H), 1.54 (s, 9H), 1.27 (d, *J* = 6.4 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$)**:** δ 149.6, 134.7, 132.4, 131.5, 130.8, 129.6, 126.3, 122.6, 118.9, 115.1, 107.4, 83.7, 68.9, 28.1, 23.5. **HRMS-ESI$^+$** m/z calculated for $C_{17}H_{21}NO_3Na$ **[M+Na]$^+$**: 310.1413, found 310.1427.

From **(±)-IV-7b** (3.5 g, 16.2 mmol), following the general procedure described above, compound **IV-7b** (1.4 g, 6.5 mmol) was obtained in 40% yield as a pale yellow oil after flash column chromatography (Cy/EtOAc, 85/15). Compound **IV-7b** was obtained in 99:1 enantiomeric ratio determined by HPLC using Chiralpak-IA column [Hexane/iPrOH (98:2)], 1.0 mL/min, τ_{major} = 8.8 min, τ_{minor} = 12.0 min. **$[\alpha]^{20}_D$** = –21.6 (*c* = 1.0, $CHCl_3$).

(–)-(*S*,*E*)-4-(4-(Methylthio)phenyl)but-3-en-2-ol, **IV-7c**.



IV-7c

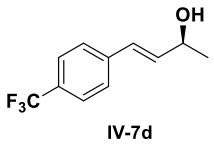
From methyl (*E*)-4-(4-(methylthio)phenyl)but-3-en-2-one (5.76 g, 30.0 mmol), following the general procedure described above, compound **IV-7c** was obtained in 85% yield as a white solid after flash column chromatography (Cy/EtOAc, 70/30).

^{1}H NMR, **^{13}C NMR** and **MS** data were consistent with literature values.[34] **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 7.30 (d, *J* = 8.4 Hz, 2H), 7.20 (d, *J* = 8.4 Hz, 2H), 6.52 (d, *J* = 15.9 Hz, 1H), 6.22 (dd, *J* = 15.9, 6.4 Hz, 1H), 4.48 (quint, *J* = 7.1, 6.6 Hz, 1H), 2.48 (s, 3H), 1.37 (d, *J* = 6.4 Hz, 3H).

[34] Zhou, Q.; Srinivas, H. D.; Zhang, S.; Watson, M. P. *J. Am. Chem. Soc.* **2016**, *138*, 11989.

From **(±)-IV-7c** (2.0 g, 10.3 mmol), following the general procedure described above, compound **IV-7c** (0.95 g, 4.9 mmol) was obtained in 47% yield as a pale yellow oil after flash column chromatography (Cy/EtOAc, 90/10). Compound **IV-7c** was obtained in 99:1 enantiomeric ratio determined by HPLC using Chiralpak-IC column [Hexane/iPrOH (95:5)], 1.0 mL/min, τ_{major} = 11.4 min, τ_{minor} = 9.7 min. $\mathbf{[\alpha]^{20}_D}$ = –33.8 (*c* = 1.0, $CHCl_3$).

(–)-(*S*,*E*)-4-(4-(Trifluoromethyl)phenyl)but-3-en-2-ol, **IV-7d**.



IV-7d

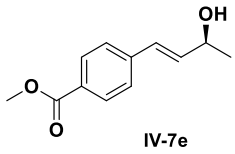
From (*E*)-4-(4-(trifluoromethyl)phenyl)but-3-en-2-one (3.76 g, 17.5 mmol), following the general procedure described above, compound **(±)-IV-7d** (3.7 g, 17.3 mmol) was obtained in 99% yield as a pale yellow oil after flash column chromatography (Cy/EtOAc, 90/10).

^{1}H NMR, **^{13}C NMR** and **MS** data were consistent with literature values.[35] **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 7.56 (d, *J* = 7.9 Hz, 2H), 7.45 (d, *J* = 7.9 Hz, 2H), 6.60 (d, *J* = 15.7 Hz, 1H), 6.35 (dd, *J* = 15.2, 5.8 Hz, 1H), 4.52 (quint, *J* = 7.7 Hz, 1H), 1.93 (s broad, 1H), 1.39 (d, *J* = 6.4 Hz, 3H).

From **(±)-IV-7d** (3.2 g, 14.8 mmol), following the general procedure described above, compound **IV-7d** (1.2 g, 5.3 mmol) was obtained in 36% yield as a pale yellow oil after flash column chromatography (Cy/EtOAc, 90/10). Compound **IV-7d** was obtained in 99:1 enantiomeric ratio determined by HPLC using Chiralpak-IA column [Hexane/iPrOH (99:1)], 1.0 mL/min, τ_{major} = 12.1 min, τ_{minor} = 10.9 min. $\mathbf{[\alpha]^{20}_D}$ = –13.4 (*c* = 1.0, $CHCl_3$).

[35] Zhang, Z.; Lee, S. D.; Fisher, A. S.; Widenhoefer, R. A. *Tetrahedron*, **2009**, *65*, 1794.

(–)-Methyl (*S*,*E*)-4-(3-hydroxybut-1-en-1-yl)benzoate, **IV-7e**.



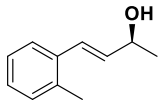
IV-7e

From methyl (*E*)-4-(3-oxobut-1-en-1-yl)benzoate (5.49 g, 27.0 mmol), following the general procedure described above, compound **IV-7e** was obtained in 88% yield as a pale yellow oil after flash column chromatography (Cy/EtOAc, 70/30).

^{1}H NMR, **^{13}C NMR** and **MS** data were consistent with literature values.[36] **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 7.97 (d, *J* = 8.4 Hz, 2H), 7.41 (d, *J* = 8.3 Hz, 2H), 6.60 (d, *J* = 16.0 Hz, 1H), 6.37 (dd, *J* = 15.9, 6.0 Hz, 1H), 4.51 (quint, *J* = 6.4 Hz, 1H), 3.90 (s, 3H), 1.38 (d, *J* = 6.4 Hz, 3H).

From **(±)-IV-7e** (2.0 g, 9.7 mmol), following the general procedure described above, compound **IV-7e** (0.93 g, 4.5 mmol) was obtained in 46% yield as a pale yellow oil after flash column chromatography (Cy/EtOAc, 90/10). Compound **IV-7e** was obtained in 99:1 enantiomeric ratio determined by HPLC using Chiralpak-IA column [Hexane/iPrOH (95:5)], 1.0 mL/min, τ_{major} = 12.9 min, τ_{minor} = 15.7 min. **$[\alpha]^{20}_D$** = –30.4 (*c* = 1.0, $CHCl_3$).

(–)-(*S*,*E*)-4-(o-Tolyl)but-3-en-2-ol, **IV-7f**.



IV-7f

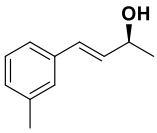
From (*E*)-4-(*o*-tolyl)but-3-en-2-one (2.60 g, 16.2 mmol), following the general procedure described above, compound **(±)-IV-7f** (1.7 g, 10.2 mmol) was obtained in 63% yield as a pale yellow oil after flash column chromatography (Cy/EtOAc, 90/10).

[36] Chen, F.; Zhang, Y.; Yu, L.; Zhu, S. *Angew. Chem. Int. Ed.* **2017**, *56*, 2022.

^{1}H NMR, **^{13}C NMR** and **MS** data were consistent with literature values.[37] **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 7.45-7.43 (m, 1H), 7.18-7.15 (m, 3H), 6.79 (d, *J* = 16.3, 1H), 6.16 (dd, *J* = 16.2, 6.7 Hz, 1H), 4.51 (quint, *J* = 6.4 Hz, 1H), 2.35 (s, 3H), 1.39 (d, *J* = 6.3 Hz, 3H).

From **(±)-IV-7f** (2.2 g, 13.5 mmol), following the general procedure described above, compound **IV-7f** (0.9 g, 5.7 mmol) was obtained in 42% yield as a pale yellow oil after flash column chromatography (Cy/EtOAc, 90/10). Compound **IV-7f** was obtained in 99:1 enantiomeric ratio determined by HPLC using Chiralpak-IG column [Hexane/iPrOH (99:1)], 1.0 mL/min, τ_{major} = 12.1 min, τ_{minor} = 10.8 min. **$[\alpha]^{20}_{D}$** = –15.7 (*c* = 1.0, $CHCl_3$).

(–)-(*S*,*E*)-4-(*m*-Tolyl)but-3-en-2-ol, **IV-7g**.



IV-7g

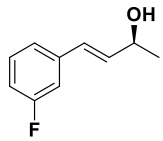
From (*E*)-4-(*m*-tolyl)but-3-en-2-one (4.37 g, 27.3 mmol), following the general procedure described above, compound **IV-7g** was obtained in 82% yield as a pale yellow oil after flash column chromatography (Cy/EtOAc, 90/10).

^{1}H NMR, **^{13}C NMR** and **MS** data were consistent with literature values.[37] **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 7.28-7.19 (m, 3H), 7.07 (d, *J* = 6.1 Hz, 1H), 6.53 (d, *J* = 16.1, 1H), 6.25 (dd, *J* = 15.8, 6.5 Hz, 1H), 4.50 (sext, *J* = 6.1 Hz, 1H), 2.36 (s, 3H), 1.57 (d, *J* = 4.2 Hz, 1H), 1.38 (d, *J* = 6.3 Hz, 3H).

From **(±)-IV-7g** (2 g, 12.3 mmol), following the general procedure described above, compound **IV-7g** (0.88 g, 5.4 mmol) was obtained in 44% yield as a pale yellow oil after flash column chromatography (Cy/EtOAc, 90/10). Compound **IV-7g** was obtained in 99:1 enantiomeric ratio

determined by HPLC using Chiralpak-IBN column [Hexane/iPrOH (99:1)], 1.0 mL/min, τ_{major} = 21.1 min, τ_{minor} = 13.4 min. **[α]$^{20}_{D}$** = –27.8 (*c* = 1.0, $CHCl_3$).

(–)-(*S*,*E*)-4-(3-Fluorophenyl)but-3-en-2-ol, **IV-7h**.



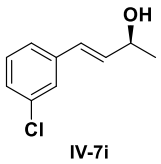
IV-7h

From (*E*)-4-(3-(fluoromethyl)phenyl)but-3-en-2-one (4.92 g, 30 mmol), following the general procedure described above, compound **(±)-IV-7h** was obtained in 93% yield as a pale yellow oil after flash column chromatography (Cy/EtOAc, 80/20).

^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.33 – 7.21 (m, 1H), 7.17 – 7.04 (m, 2H), 6.94 (m, 1H), 6.55 (d, *J* = 15.9 Hz, 1H), 6.27 (dd, *J* = 15.9, 6.1 Hz, 1H), 4.50 (quintd, *J* = 6.3, 1.3 Hz, 1H), 1.79 (s, 1H), 1.38 (d, *J* = 6.4 Hz, 3H). **^{13}C-NMR** (76 MHz, CDCl3) δ 163.2 (d, $J_{C\text{-}F}$ = 245 Hz), 139.3 (d, $J_{C\text{-}F}$ = 8 Hz) 135.10, 130.1(d, $J_{C\text{-}F}$ = 8 Hz), 128.3 (d, $J_{C\text{-}F}$ = 3 Hz), 122.5 (d, $J_{C\text{-}F}$ = 3 Hz), 114.5 (d, $J_{C\text{-}F}$ = 21 Hz), 113.0 (d, $J_{C\text{-}F}$ = 22 Hz), 68.76, 23.52. **HRMS-EI^{+}** m/z calculated for $C_{10}H_{11}OF$ **[M]$^{+}$**: 166.0794, found 166.0790.

From **(±)-IV-7h** (1.7 g, 10.3 mmol), following the general procedure described above, compound **IV-7h** (0.75 g, 4.5 mmol) was obtained in 44% yield as a pale yellow oil after flash column chromatography (Cy/EtOAc, 90/10). Compound **IV-7h** was obtained in 99:1 enantiomeric ratio determined by HPLC using Chiralpak-IBN column [Hexane/iPrOH (95:5)], 1.0 mL/min, τ_{major} = 8.5 min, τ_{minor} = 6.3 min. **[α]$^{20}_{D}$** = –19.0 (*c* = 1.0, $CHCl_3$).

(–)-(*S*,*E*)-4-(3-Chlorophenyl)but-3-en-2-ol, **IV-7i**.



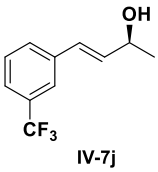
IV-7i

From (*E*)-4-(3-chlorophenyl)but-3-en-2-one (3.15 g, 17.4 mmol), following the general procedure described above, compound **(±)-IV-7i** was obtained in 92% yield as a pale yellow oil after flash column chromatography (Cy/EtOAc, 90/10).

^{1}H NMR, **^{13}C NMR** and **MS** data were consistent with literature values.[37] **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 7.36 (s broad, 1H), 7.27-7.19 (m, 3H), 6.52 (dd, *J* = 15.9, 1.3 Hz, 1H), 6.27 (dd, *J* = 15.9, 6.3 Hz, 1H), 4.54-4.45 (quint, *J* = 6.5, 1.2 Hz, 1H), 1.74 (s broad, 1H), 1.38 (d, *J* = 6.5 Hz, 3H).

From **(±)-IV-7i** (2.8 g, 15.3 mmol), following the general procedure described above, compound **IV-7i** (1.1 g, 5.8 mmol) was obtained in 38% yield as a pale yellow oil after flash column chromatography (Cy/EtOAc, 90/10). Compound **IV-7i** was obtained in 99:1 enantiomeric ratio determined by HPLC using Chiralpak-IBN column [Hexane/iPrOH (98:2)], 1.0 mL/min, τ_{major} = 25.0 min, τ_{minor} = 12.3 min. **$[\alpha]^{20}_D$** = –17.3 (*c* = 1.0, $CHCl_3$).

(–)-(*S*,*E*)-4-(3-(Trifluoromethyl)phenyl)but-3-en-2-ol, **IV-7j**.



IV-7j

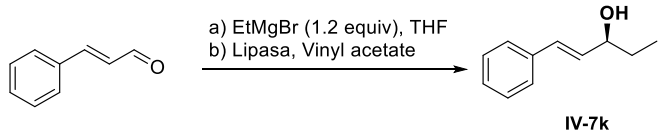
From (*E*)-4-(3-(trifluoromethyl)phenyl)but-3-en-2-one (5.73 g, 26.7 mmol), following the general procedure described above, compound **(±)-IV-7j** (5.6 g, 25.9 mmol) was obtained in 97% yield as a pale yellow oil after flash column chromatography (Cy/EtOAc, 90/10).

[37] Li, X.; Li, L.; Tang, Y.; Zhong, L.; Cun, L.; Zhu, J.; Liao, J.; Deng, J. *J. Org. Chem.* **2010**, *75*, 2981.

^{1}H NMR, **^{13}C NMR** and **MS** data were consistent with literature values.[38] **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 7.62 (s, 1H), 7.56-7.40 (m, 3H), 6.62 (d, *J* = 15.8, 1H), 6.35 (dd, *J* = 15.8, 6.2 Hz, 1H), 4.53 (s broad, 1H), 1.39 (d, *J* = 6.2 Hz, 3H).

From **(±)-IV-7j** (3.5 g, 16.2 mmol), following the general procedure described above, compound **IV-7j** (1.4 g, 6.5 mmol) was obtained in 40% yield as a pale yellow oil after flash column chromatography (Cy/EtOAc, 90/10). Compound **IV-7j** was obtained in 99:1 enantiomeric ratio determined by HPLC using Chiralpak-IA column [Hexane/iPrOH (99:1)], 1.0 mL/min, τ_{major} = 8.7 min, τ_{minor} = 8.1 min. **$[\alpha]^{20}_D$** = –19.0 (*c* = 1.0, $CHCl_3$).

*4.5.1.3. Synthesis of (–)-(S,E)-1-phenylpent-1-en-3-ol, **IV-7k**.*



To a solution of cinnamaldehyde (6.61 g, 30.0 mmol, 1 equiv) in THF (90 mL) at 0 ºC, was added dropwise a solution of ethylmagnesium bromide (36 mmol, 1.2 equiv, 1M in THF). The reaction was stirred at 0 ºC for 2 h and then was allowed to warm to room temperature and stirred overnight. The reaction mixture was quenched with water and extracted with diethyl ether for three times, dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography on silica gel. Compound **(±)-IV-7k** was obtained in 92%

[38] Sgalla, S.; Fabrizi, G.; Cirilli, R.; Macone, A.; Bonamore, A.; Boffic, A.; Cacchia, S. Tetrahedron: Asymmetry, **2007**, *18*, 2791.

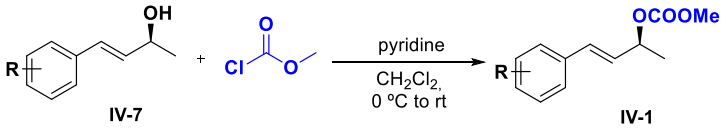
yield as a yellowish oil after flash column chromatography (Cy/EtOAc, 80/20).

^{1}H NMR, **^{13}C NMR** and **MS** data were consistent with literature values.[37] **^{1}H-RMN** (300 MHz, $CDCl_3$): δ 7.42-7.24 (m, 5H), 6.58 (d, *J* = 16.3, 1H), 6.23 (dd, *J* = 15.9, 6.6 Hz, 1H), 4.23 (m, 1H), 1.69 (m, 3H), 1.00 (t, *J* = 7.4 Hz, 3H).

The enantiopure allylic alcohol was obtained from the kinetic resolution using Amano Lipase from Pseudomonas fluorescens following the previous procedure.[32]

From **(±)-IV-7k** (2.0 g, 12.3 mmol), following the general procedure described above, compound **IV-7k** (0.99 g, 5.0 mmol) was obtained in 50% yield as a pale yellow oil after flash column chromatography (Cy/EtOAc, 95/5). Compound **IV-7k** was obtained in 99:1 enantiomeric ratio determined by HPLC using Chiralpak-IC column [Hexane/iPrOH (95:5)], 1.0 mL/min, τ_{major} = 5.8 min, τ_{minor} = 5.1 min. **$[\alpha]^{20}_{D}$** = –32.7 (*c* = 1.0, $CHCl_3$).

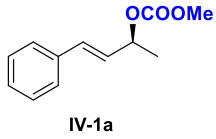
*4.5.1.4. Synthesis of allylic carbonates, **IV-1**.*



To a solution of the corresponding alcohol **IV-7** (1 equiv) and pyridine (3 equiv) in CH_2Cl_2 (0.2M) at 0 ºC was added dropwise methyl chloroformate (2 equiv). The reaction mixture was allowed to warm to room temperature and stirred overnight. The reaction was quenched by addition of 1M HCl aqueous solution and extracted three times with Et_2O,

dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography on silica gel using the appropriate mixture of solvents.[39]

(–)-(*S*,*E*)-Methyl (4-phenylbut-3-en-2-yl) carbonate, **IV-1a**.



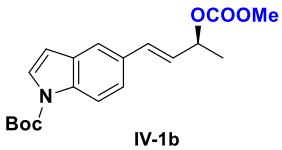
IV-1a

From (*S*,*E*)-4-phenylbut-3-en-2-ol (1.51 g, 10.2 mmol), following the general procedure described above, compound **IV-1a** (1.9 g, 9.4 mmol) was obtained in 92% yield as a colorless oil after flash column chromatography (Cy/EtOAc, 90/10).

^{1}H NMR, **^{13}C NMR** and **MS** data were consistent with literature values.[40] **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 7.45-7.28 (m, 5H), 6.67 (d, *J* = 15.9 Hz, 1H), 6.23 (d, *J* = 16.0, 7.1 Hz, 1H), 5.43 (quint, *J* = 6.2 Hz, 1H), 3.83 (s, 3H), 1.51 (d, *J* = 6.5 Hz, 3H).

Compound **IV-1a** was obtained in 99:1 enantiomeric ratio determined by HPLC using Chiralpak-IA column [Hexane/iPrOH (99:1)], 1.0 mL/min, τ_{major} = 3.5 min, τ_{minor} = 3.1 min. **$[\alpha]^{20}_D$** = –117.4 (*c* = 1.0, $CHCl_3$).

(–)-*tert*-Butyl-(*S*,*E*)-5-(3-((methoxycarbonyl)oxy)but-1-en-1-yl)-1H-indole-1-carboxylate, **IV-1b**.



IV-1b

From *tert*-butyl (*S*,*E*)-5-(3-hydroxybut-1-en-1-yl)-1H-indole-1-carboxylate (0.7 g, 2.5 mmol), following the general procedure described above, compound **IV-1b** was

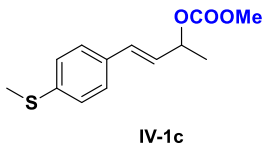
[39] Li, C.; Breit, B. *Chem. Eur.J.* **2016**, *22*, 14655.
[40] Trost, B. M.; Richardson, J.; Yong, K. *J. Am. Chem. Soc.* **2006**, *128*, 2540.

obtained in 91% yield as a pale yellow oil after flash column chromatography (Cy/EtOAc, 90/10).

^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.07 (d, *J* = 8.5 Hz, 1H), 7.57 (m, 2H), 7.38 (d, *J* = 8.5 Hz, 1H), 6.73 (d, *J* = 15.8 Hz, 1H), 6.55 (d, *J* = 3.7 Hz, 1H), 6.20 (dd, *J* = 15.9, 7.1 Hz, 1H), 5.42 (quint, *J* = 6.5 Hz, 1H), 3.81 (s, 3H), 1.69 (s, 9H), 1.50 (d, *J* = 6.2 Hz, 3H). **^{13}C-NMR** (75 MHz, $CDCl_3$): δ 155.2, 149.5, 135.1, 132.8, 130.9, 130.8, 126.8, 126.4, 122.9, 119.4, 115.2, 107.3, 83.7, 75.6, 54.5, 28.1, 20.5. **HRMS-ESI^{+}** m/z calculated for $C_{19}H_{23}NO_5Na$ **[M+Na]$^{+}$**: 368.1492, found 368.1483.

Compound **IV-1b** was obtained in 97:3 enantiomeric ratio determined by HPLC using Chiralpak-IA column [Hexane/iPrOH (99:1)], 1.0 mL/min, τ_{major} = 6.0 min, τ_{minor} = 5.3 min. **$[\alpha]^{20}_{D}$** = –79.6 (*c* = 1.0, $CHCl_3$).

(–)-(*S*,*E*)-Methyl (4-(4-(methylthio)phenyl)but-3-en-2-yl) carbonate, **IV-1c**.



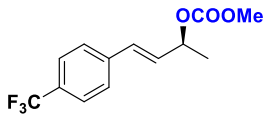
IV-1c

From (*S*,*E*)-4-(4-(methylthio)phenyl)but-3-en-2-ol (693 mg, 3.6 mmol), following the general procedure described above, compound **IV-1c** was obtained in 52% yield as a pale yellow oil after flash column chromatography (Cy/EtOAc, 90/10).

^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.30 (d, *J* = 8.4 Hz, 2H), 7.19 (d, *J* = 8.4 Hz, 2H), 6.59 (d, *J* = 16.0 Hz, 1H), 6.15 (dd, *J* = 15.9, 7.0 Hz, 1H), 5.36 (m, 1H), 3.78 (s, 3H), 2.48 (s, 3H), 1.46 (d, *J* = 6.5 Hz, 3H). **^{13}C-NMR** (75 MHz, $CDCl_3$): δ 155.3, 138.6, 133.2, 131.8, 127.6, 127.2, 126.7, 75.5, 54.8, 20.6, 15.9. **HRMS-ESI^{+}** m/z calculated for $C_{13}H_{16}O_3SNa$ **[M+Na]$^{+}$**: 275.0712, found 275.0717.

Compound **IV-1c** was obtained in 99:1 enantiomeric ratio determined by HPLC using Chiralpak-IC column [Hexane/iPrOH (99:1)], 1.0 mL/min, τ_{major} = 5.6 min, τ_{minor} = 5.2 min. **[α]$^{20}_{D}$** = –105.3 (*c* = 1.0, $CHCl_3$).

(–)-(*S*,*E*)-4-(4-Trifluorophenyl)but-3-en-2-yl methyl carbonate, **IV-1d**.



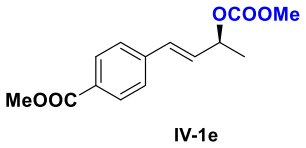
IV-1d

From (*S*,*E*)-4-(3-fluorophenyl)but-3-en-2-ol (780 mg, 3.6 mmol), following the general procedure described above, compound **IV-1d** was obtained in 76% yield as a pale yellow oil after flash column chromatography (Cy/EtOAc, 95/5).

^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.26 – 7.15 (m, 1H), 7.12 – 6.96 (m, 2H), 6.92 – 6.82 (m, 1H), 6.54 (d, *J* = 16.0 Hz, 1H), 6.13 (dd, *J* = 16.0, 6.8 Hz, 1H), 5.29 (m, 1H), 3.72 (s, 3H), 1.40 (d, *J* = 6.5, 3H). **^{13}C-NMR** (75 MHz, $CDCl_3$): δ 155.1, 139.7 (q, $J_{C\text{-}F}$ = 1 Hz), 130.8, 130.6, 129.8 (q, $J_{C\text{-}F}$ = 32 Hz), 126.8, 124.1 (q, $J_{C\text{-}F}$ = 271 Hz), 125.5 (q, $J_{C\text{-}F}$ = 4 Hz), 74.7, 54.7, 20.3. **HRMS-ESI^{+}** m/z calculated for $C_{13}H_{13}O_3F_3Na$ **[M+Na]$^{+}$**: 297.0709, found 297.0715.

Compound **IV-1d** was obtained in 99:1 enantiomeric ratio determined by HPLC using Chiralpak-IA column [Hexane/iPrOH (99:1)], 1.0 mL/min, τ_{major} = 4.4 min, τ_{minor} = 3.4 min. **[α]$^{20}_{D}$** = –132.7 (*c* = 1.0, $CHCl_3$).

(–)-Methyl (*S*,*E*)-4-(3-((methoxycarbonyl)oxy)but-1-en-1-yl)benzoate, **IV-1e**.



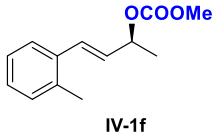
IV-1e

From methyl (*S*,*E*)-4-(3-hydroxybut-1-en-1-yl)benzoate (850 mg, 4.1 mmol), following the general procedure described above, compound **IV-1e** was obtained in 67% yield as a pale yellow oil after flash column chromatography (Cy/EtOAc, 90/10).

^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.99 (d, *J* = 8.4 Hz, 2H), 7.44 (d, *J* = 8.1 Hz, 2H), 6.68 (d, *J* = 16.3 Hz, 1H), 6.31 (dd, *J* = 16.0, 6.7 Hz, 1H), 5.39 (quintd, *J* = 6.5, 1.2 Hz, 1H), 3.92 (s, 3H), 3.80 (s, 3H), 1.49 (d, *J* = 6.5 Hz, 3H). **^{13}C-NMR** (75 MHz, $CDCl_3$): δ 166.9, 155.2, 140.8, 131.2, 130.9, 130.1, 129.6, 126.7, 75.0, 54.8, 52.2, 20.5. **HRMS-ESI^{+}** m/z calculated for $C_{14}H_{16}O_5Na$ **[M+Na]$^{+}$:** 287.0889, found 287.0903.

Compound **IV-1e** was obtained in 99:1 enantiomeric ratio determined by HPLC using Chiralpak-IBN column [Hexane/iPrOH (99:1)], 1.0 mL/min, τ_{major} = 7.9 min, τ_{minor} = 6.7 min. **[α]$^{20}_{D}$** = –89.4 (*c* = 1.0, $CHCl_3$).

(–)-(*S*,*E*)-Methyl (4-(*o*-tolyl)but-3-en-2-yl) carbonate, **IV-1f**.



IV-1f

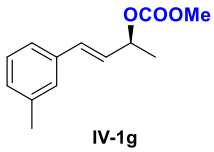
From (*S*,*E*)-4-(*o*-tolyl)but-3-en-2-ol (0.2 g, 1.2 mmol), following the general procedure described above, compound **IV-1f** (0.26 g, 1.2 mmol) was obtained in 99% yield as a colorless oil after flash column chromatography (Cy/EtOAc, 90/10).

^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.42 (s broad, 1H), 7.15 (m, 2H), 6.85 (d, *J* = 16.0 Hz, 1H), 6.06 (dd, *J* = 16.1, 6.7 Hz, 1H), 6.39 (m, 1H), 3.79 (s, 3H), 2.35 (s, 3H), 1.47 (d, *J* = 6.9 Hz, 3H). **^{13}C-NMR** (75 MHz, $CDCl_3$): δ 155.2, 135.8, 135.3, 130.3, 130.2, 129.5, 127.9, 126.1, 125.8, 75.5, 54.5,

20.5, 19.7. **HRMS-ESI**$^{+}$ m/z calculated for $C_{13}H_{16}O_3Na$ **[M+Na]**$^{+}$: 243.0991, found 243.0997.

Compound **IV-1f** was obtained in 99:1 enantiomeric ratio determined by HPLC using Chiralpak-IG column [Hexane/iPrOH (99:1)], 1.0 mL/min, τ_{major} = 3.3 min, τ_{minor} = 3.1 min. **[α]$^{20}_{D}$** = –93.2 (*c* = 1.0, $CHCl_3$).

(–)-(*S*,*E*)-Methyl (4-(*m*-tolyl)but-3-en-2-yl) carbonate, **IV-1g**.



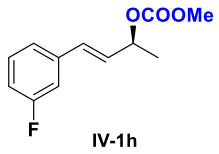
IV-1g

From (*S*,*E*)-4-(*m*-tolyl)but-3-en-2-ol (400 mg, 2.5 mmol), following the general procedure described above, compound **IV-1g** (312 mg, 1.4 mmol) was obtained in 57% yield as a pale yellow oil after flash column chromatography (Cy/EtOAc, 95/5).

^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.24 – 7.16 (m, 3H), 7.13 – 7.02 (m, 1H), 6.62 (dd, *J* = 15.9, 1.1 Hz, 1H), 6.19 (dd, *J* = 15.9, 7.0 Hz, 1H), 5.45 – 5.28 (m, 1H), 3.78 (s, 3H), 2.34 (s, 3H), 1.47 (d, *J* = 6.4 Hz, 3H).**^{13}C-NMR** (75 MHz, $CDCl_3$): δ 155.3 138.3, 136.3, 132.5, 129.0, 128.6, 128.0, 127.5, 124.0, 77.6, 77.2, 76.7, 75.5, 54.7, 21.5, 20.6. **HRMS-ESI**$^{+}$ m/z calculated for $C_{13}H_{16}O_3Na$ **[M+Na]**$^{+}$: 243.0991, found 243.1001.

Compound **IV-1g** was obtained in 99:1 enantiomeric ratio determined by HPLC using Chiralpak-IG column [Hexane/iPrOH (99.5:0.5)], 1.0 mL/min, τ_{major} = 7.2 min, τ_{minor} = 6.9 min. **[α]$^{20}_{D}$** = –96.2 (*c* = 1.0, $CHCl_3$).

(–)-(*S*,*E*)-4-(3-fluorophenyl)but-3-en-2-yl methyl carbonate, **IV-1h**.



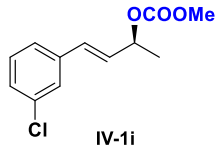
IV-1h

From (*S*,*E*)-4-(3-fluorophenyl)but-3-en-2-ol (598 g, 3.6 mmol), following the general procedure described above, compound **IV-1h** was obtained in 73% yield as a pale yellow oil after flash column chromatography (Cy/EtOAc, 95/5).

^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.26 – 7.15 (m, 1H), 7.12 – 6.96 (m, 2H), 6.92 – 6.82 (m, 1H), 6.54 (d, *J* = 16.0 Hz, 1H), 6.13 (dd, *J* = 16.0, 6.8 Hz, 1H), 5.29 (m, 1H), 3.72 (s, 3H), 1.40 (d, *J* = 6.5, 3H). **^{13}C-NMR** (75 MHz, $CDCl_3$): δ 163.2 (d, $J_{C\text{-}F}$ = 245 Hz), 155.24, 138.7 (d, $J_{C\text{-}F}$ = 8 Hz), 131.1 (d, $J_{C\text{-}F}$ = 2 Hz), 130.2 (d, $J_{C\text{-}F}$ = 3 Hz), 129.66, 122.7 (d, $J_{C\text{-}F}$ = 3 Hz), 115.0 (d, $J_{C\text{-}F}$ = 21 Hz), 113.2 (d, $J_{C\text{-}F}$ = 21 Hz), 75.02, 54.78, 20.52. **HRMS-ESI^{+}** m/z calculated for $C_{12}H_{13}O_3FNa$ **[M+Na]$^{+}$**: 247.0740, found 247.0747.

Compound **IV-1h** was obtained in 99:1 enantiomeric ratio determined by HPLC using Chiralpak-IA column [Hexane/iPrOH (99:1)], 1.0 mL/min, τ_{major} = 3.8 min, τ_{minor} = 3.2 min. **$[\alpha]^{20}_{D}$** = –92.6 (*c* = 1.0, $CHCl_3$).

(–)-(*S*,*E*)-4-(3-Chlorophenyl)but-3-en-2-yl methyl carbonate, **IV-1i**.



IV-1i

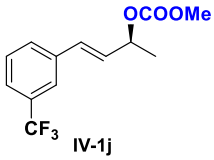
From (*S*,*E*)-4-(3-chlorophenyl)but-3-en-2-ol (0.2 g, 1.3 mmol), following the general procedure described above, compound **IV-1i** was obtained in 63% yield as a pale yellow oil after flash column chromatography (Cy/EtOAc, 90/10).

^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.39 (s broad, 1H), 7.26 (m, 3H), 6.58 (d, *J* = 16.0 Hz, 1H), 6.21 (d, *J* = 16.0, 6.6 Hz, 1H), 5.38 (quint, *J* = 6.5 Hz, 1H), 3.81 (s, 3H), 1.47 (d, *J* = 6.5 Hz, 3H). **^{13}C-NMR** (75 MHz, $CDCl_3$): δ

155.1, 138.1, 134.6, 130.4, 129.8, 129.7, 127.9 126.5, 124.9, 74.8, 54.6, 20.4. **HRMS-ESI**$^+$ m/z calculated for $C_{12}H_{13}O_3ClNa$ **[M+Na]**$^+$: 247.0496, found 247.0498.

Compound **IV-1i** was obtained in 99:1 enantiomeric ratio determined by HPLC using Chiralpak-IA column [Hexane/iPrOH (99:1)], 1.0 mL/min, τ_{major} = 3.9 min, τ_{minor} = 3.2 min. **[α]$^{20}_D$** = –119.0 (*c* = 1.0, $CHCl_3$).

(–)-(*S*,*E*)-Methyl (4-(3-(trifluoromethyl)phenyl)but-3-en-2-yl) carbonate, **IV-1j**.



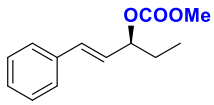
IV-1j

From (*S*,*E*)-4-(3-(trifluoromethyl)phenyl)but-3-en-2-ol (0.4 g, 1.8 mmol), following the general procedure described above, compound **IV-1j** (0.47 g, 1.71 mmol) was obtained in 95% yield as a colorless oil after flash column chromatography (Cy/EtOAc, 90/10).

^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.65 (s, 1H), 7.51 (m, 3H), 6.65 (d, *J* = 16.0 Hz, 1H), 6.27 (dd, *J* = 15.8, 6.6 Hz, 1H), 5.40 (quint, *J* = 6.6 Hz, 1H), 3.81 (s, 3H), 1.49 (d, *J* = 6.5 Hz, 3H). **^{13}C-NMR** (75 MHz, $CDCl_3$): δ 155.2, 137.1, 131.2 (q, $J_{C\text{-}F}$ = 32.4 Hz), 130.7, 130.2, 129.9, 129.2, 125.9 (q, $J_{C\text{-}F}$ = 272.6 Hz), 124.6 (q, $J_{C\text{-}F}$ = 3.9 Hz), 123.4 (q, *J* = 3.9 Hz), 74.9, 54.7, 20.4. **HRMS-ESI**$^+$ m/z calculated for $C_{13}H_{13}O_3F_3Na$ **[M+Na]**$^+$: 297.0709, found 297.0720.

Compound **IV-1j** was obtained in 99:1 enantiomeric ratio determined by HPLC using Chiralpak-IA column [Hexane/iPrOH (99:1)], 1.0 mL/min, τ_{major} = 3.4 min, τ_{minor} = 2.9 min. **[α]$^{20}_D$** = –82.5 (*c* = 1.0, $CHCl_3$).

(–)-(*S*,*E*)-Methyl (1-phenylpent-1-en-3-yl) carbonate, **IV-1k**.



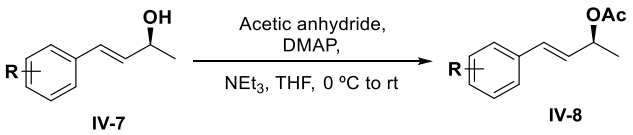
IV-1k

From (*S*,*E*)-1-phenylpent-1-en-3-ol (1.5 g, 9.2 mmol), following the general procedure described above, compound **IV-1k** was obtained in 74% yield as a pale yellow oil after flash column chromatography (Cy/EtOAc, 95/5).

^{1}H NMR, **^{13}C NMR** and **MS** data were consistent with literature values.[41] **^{1}H-RMN** (300 MHz, $CDCl_3$): δ 7.43-7.26 (m, 5H), 6.65 (d, *J* = 16.6 Hz, 1H), 6.14 (dd, *J* = 16.2, 7.6 Hz, 1H), 5.17 (q, *J* = 6.7 Hz, 1H), 3.80 (s, 3H), 1.81 (m, 2H), 0.99 (t, *J* = 7.3 Hz, 3H).

Compound **IV-1k** was obtained in 99:1 enantiomeric ratio determined by HPLC using Chiralpak-IA column [Hexane/iPrOH (99:1)], 1.0 mL/min, τ_{major} = 3.5 min, τ_{minor} = 3.2 min. **[α]$^{20}_D$**= –113.1 (*c* = 1.0, $CHCl_3$).

*4.5.1.5. Synthesis of allylic acetates **IV-8**.*



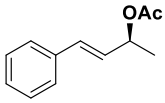
IV-7 **IV-8**

The enantiopure allylic acetates were prepared following the described procedure starting from the corresponding alcohols **IV-7**.[42] Alcohol **IV-7** (1 equiv) was combined with THF (7 mL/mmol alcohol), acetic anhydride (1.20 equiv), triethylamine (1.80 equiv), and DMAP (2 mol%) at 0 °C. The reaction mixture was maintained at 0 °C for 1 h and then was allowed to

[41] Yamada, Y. M. A.; Sarkar, S. M.; Uozumi, Y. *J. Am. Chem.Soc.* **2012**, *134*, 3190.
[42] Onaran, M. B.; Seto, C. T. *J. Org. Chem.* **2003**, *68*, 8136.

stir at room temperature overnight. The solvent was removed by rotary evaporation, and the resulting material was washed with water, brine and dried over $MgSO_4$. Purification by flash column chromatography gave the desired product.

(–)-(*S*,*E*)-4-Phenylbut-3-en-2-yl acetate, **IV-8a**.



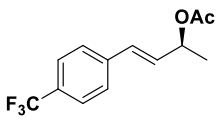
IV-8a

From (*S*,*E*)-4-(phenyl)but-3-en-2-ol (0.84 g, 5.7 mmol), following the general procedure described above, compound **IV-8a** (0.81 g, 4.3 mmol) was obtained in 75% yield as a pale yellow oil after flash column chromatography (Cy/AcOEt, 90/10).

^{1}H NMR, **^{13}C NMR** and **MS** data were consistent with literature values.[22] **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 7.46 – 7.40 (m, 2H), 7.40 – 7.33 (m, 2H), 7.33 – 7.28 (m, 1H), 6.65 (d, *J* = 16.0 Hz, 1H), 6.23 (dd, *J* = 16.0, 6.7 Hz, 1H), 5.57 (quint, *J* = 6.5 Hz, 1H), 2.12 (s, 3H), 1.45 (d, *J* = 6.5 Hz, 3H).

Compound **IV-8a** was obtained in 99:1 enantiomeric ratio determined by HPLC using Chiralpak-IC column [Hexane/iPrOH (99.5:0.5)], 1.0 mL/min, τ_{major} = 8.2 min, τ_{minor} = 6.0 min. **$[\alpha]^{20}_D$** = –169.6 (*c* = 1.0, $CHCl_3$).

(–)-(*S*,*E*)-4-(4-(Trifluoromethyl)phenyl)but-3-en-2-yl acetate, **IV-8d**.



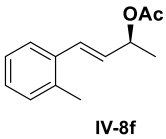
IV-8d

From (*S*,*E*)-4-(4-(trifluoromethyl)phenyl)but-3-en-2-ol (0.6 g, 2.83 mmol), following the general procedure described above, compound **IV-8d** (0.69 g, 2.68 mmol) was obtained in 95% yield as a pale yellow oil after flash column chromatography (Cy/AcOEt, 90/10).

^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.56 (d, *J* = 8.3 Hz, 2H), 7.47 (d, *J* = 8.3 Hz, 2H), 6.62 (d, *J* = 16.0 Hz, 1H), 6.28 (dd, *J* = 16.0, 6.5 Hz, 1H), 5.54 (quint, *J* = 6.5 Hz, 1H), 2.09 (s, 3H), 1.42 (d, *J* = 6.5 Hz, 3H).**^{13}C-NMR** (75 MHz, $CDCl_3$): δ 170.4, 140.0 (q, $J_{C\text{-}F}$ = 1.5 Hz), 131.7, 130.1, 129.9 (q, $J_{C\text{-}F}$ = 32.5 Hz), 126.9, 125.7 (q, $J_{C\text{-}F}$ = 4.8 Hz), 124.3 (q, $J_{C\text{-}F}$ = 247 Hz), 70.7, 21.5, 20.4. **HRMS-EI^{+}** m/z calculated for $C_{13}H_{13}O_2F_3$ **[M]$^{+}$:** 258.0868, found 258.0871.

Compound **IV-8d** was obtained in 99:1 enantiomeric ratio determined by HPLC using Chiralpak-IA column [Hexane/iPrOH (99.5:0.5)], 1.0 mL/min, τ_{major} = 5.3 min, τ_{minor} = 4.0 min. **[α]$^{20}_{D}$** = –135.7 (*c* = 1.0, $CHCl_3$).

(–)-(*S*,*E*)-4-(*o*-Tolyl)but-3-en-2-yl acetate, **IV-8f**.



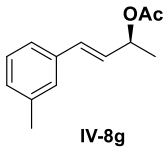
IV-8f

From (*S*,*E*)-4-(*o*-tolyl)but-3-en-2-ol (1.0 g, 6.2 mmol), following the general procedure described above, compound **IV-8f** (1.1 g, 5.4 mmol) was obtained in 87% yield as a pale yellow oil after flash column chromatography (Cy/AcOEt, 90/10).

^{1}H-NMR (300 MHz, $CDCl_3$): δ 1H NMR (300 MHz, Chloroform-d) δ 7.42 (m, 1H), 7.16 (m, 3H), 6.83 (d, *J* = 15.8 Hz, 1H), 6.07 (dd, *J* = 15.8, 6.8 Hz, 1H), 5.55 (quint, *J* = 6.2 Hz, 1H), 2.35 (s, 3H), 2.08 (s, 3H), 1.43 (d, *J* = 6.5 Hz, 3H). **^{13}C-NMR** (75 MHz, $CDCl_3$): δ 170.5, 135.8, 135.6, 130.4, 130.3, 129.6, 127.9, 126.2, 125.8, 71.4, 21.5, 20.6, 19.9. **HRMS-GCEI^{+}** m/z calculated for $C_{13}H_{16}O_2$ **[M]$^{+}$:** 204.1150, found 204.1144.

Compound **IV-8f** was obtained in 99:1 enantiomeric ratio determined by HPLC using Chiralpak-IBN column [Hexane/iPrOH (99.5:0.5)], 1.0 mL/min, τ_{major} = 5.8 min, τ_{minor} = 5.3 min. **[α]$^{20}_{D}$** = –83.6 (*c* = 1.0, $CHCl_3$).

(–)-(*S*,*E*)-4-(*m*-Tolyl)but-3-en-2-yl acetate, **IV-8g**.



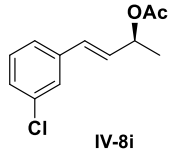
IV-8g

From (*S*,*E*)-4-(*m*-tolyl)but-3-en-2-ol (0.40 g, 2.5 mmol), following the general procedure described above, compound **IV-8g** (0.46 g, 2.25 mmol) was obtained in 92% yield as a pale yellow oil after flash column chromatography (Cy/AcOEt, 90/10).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.11 (m, 3H), 6.98 (d, *J* = 6.7 Hz, 1H), 6.49 (d, *J* = 16.0 Hz, 1H), 6.09 (dd, *J* = 16.0, 6.7 Hz, 1H), 5.44 (quint, *J* = 6.5 Hz, 1H), 2.26 (s, 3H), 1.99 (s, 3H), 1.33 (d, *J* = 6.5 Hz, 3H). **^{13}C-NMR** (76 MHz, CDCl3) δ 170.4, 138.2, 136.4, 131.8, 128.8, 128.8, 128.6, 127.4, 123.9, 71.2, 21.5, 21.5, 20.5. **HRMS-GCEI^{+}** m/z calculated for $C_{13}H_{16}O_2$ **[M]$^{+}$:** 204.1150, found 204.1142.

Compound **IV-8g** was obtained in 99:1 enantiomeric ratio determined by HPLC using Chiralpak-IC column [Hexane/iPrOH (99.5:0.5)], 1.0 mL/min, τ_{major} = 9.2 min, τ_{minor} = 6.3 min. **$[\alpha]^{20}_{D}$** = –122.7 (*c* = 1.0, $CHCl_3$).

(–)-(*S*,*E*)-4-(3-Chlorophenyl)but-3-en-2-yl acetate, **IV-8i**.



IV-8i

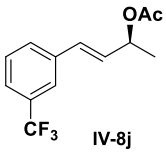
From (*S*,*E*)-4-(3-chlorophenyl)but-3-en-2-ol (0.50 g, 2.7 mmol), following the general procedure described above, compound **IV-8i** (0.38 g, 1.7 mmol) was obtained in 62% yield as a pale yellow oil after flash column chromatography (Cy/AcOEt, 90/10).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.37 (m, 1H), 7.26 – 7.18 (m, 3H), 6.53 (dd, *J* = 16.0, 0.8 Hz, 1H), 6.19 (dd, *J* = 16.0, 6.6 Hz, 1H), 5.59 – 5.42 (m, 1H), 2.08 (s, 3H), 1.40 (d, *J* = 6.5 Hz, 3H). **^{13}C-NMR** (76 MHz, $CDCl_3$) δ 170.4, 138.3, 134.6, 130.5, 130.2, 129.9, 127.9, 126.5, 125.0, 70.8, 21.5,

20.4. **HRMS-EI**$^{+}$ m/z calculated for $C_{12}H_{13}O_2Cl$ **[M]**$^{+}$: 224.0604, found 224.0594.

Compound **IV-8i** was obtained in 99:1 enantiomeric ratio determined by HPLC using Chiralpak-IC column [Hexane/iPrOH (99.5:0.5)], 1.0 mL/min, τ_{major} = 5.6 min, τ_{minor} = 4.4 min. **[α]$^{20}_{D}$** = –95.3 (*c* = 1.0, $CHCl_3$).

(–)-(*S*,*E*)-4-(3-(Trifluoromethyl)phenyl)but-3-en-2-yl acetate, **IV-8j**.



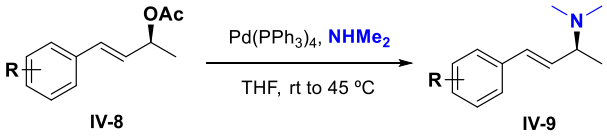
IV-8j

From (*S*,*E*)-4-(3-(trifluoromethyl)phenyl)but-3-en-2-ol (2.0 g, 9.3 mmol), following the general procedure described above, compound **IV-8j** (2.2 g, 8.5 mmol) was obtained in 92% yield as a pale yellow oil after flash column chromatography (Cy/AcOEt, 90/10).

^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.60 – 7.52 (m, 1H), 7.47 – 7.38 (m, 2H), 7.38 – 7.30 (m, 1H), 6.54 (d, *J* = 16.0 Hz, 1H), 6.18 (dd, *J* = 16.0, 6.5 Hz, 1H), 5.45 (quintd, *J* = 6.5, 1.0 Hz, 1H), 2.00 (s, 3H), 1.34 (d, *J* = 6.5 Hz, 3H). **^{13}C NMR** (76 MHz, $CDCl_3$) δ 170.4, 137.3, 131.2 (q, $J_{C\text{-}F}$ = 31.6 Hz), 131.1, 130.1, 129.9 (q, $J_{C\text{-}F}$ = 1.7 Hz), 129.2, 124.5 (q, $J_{C\text{-}F}$ = 3.8 Hz), 124.2 (q, $J_{C\text{-}F}$ = 271.3 Hz), 123.3 (q, $J_{C\text{-}F}$ = 3.8 Hz), 70.7, 31.0, 21.4, 20.4. **HRMS-EI**$^{+}$ m/z calculated for $C_{13}H_{13}O_2F_3$ **[M]**$^{+}$: 258.0868, found 258.0873.

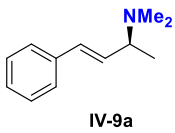
Compound **IV-8j** was obtained in 99:1 enantiomeric ratio determined by HPLC using Chiralpak-IBN column [Hexane/iPrOH (99.5:0.5)], 1.0 mL/min, τ_{major} = 3.8 min, τ_{minor} = 3.3 min. **[α]$^{20}_{D}$** = –135.5 (*c* = 1.0, $CHCl_3$).

*4.5.1.6. Synthesis of allylic amines **IV-9**.*



To a stirred solution of allylic acetate (1 equiv), $Pd(PPh_3)_4$ (0.03 equiv) and PPh_3 (0.04 equiv) in THF (2 mL/mmol) was added dimethylamine (2M THF, 2 equiv) under argon atmosphere at room temperature. The reaction mixture was stirred overnight at 45 ºC. The mixture was extracted with HCl 1M (5x). The aqueous phase was taken to basic pH using NaOH 2M and extracted with DCM (5x). The combined organic layers were dried over $MgSO_4$ and the solvent was evaporated. The crude reaction was purified by flash column chromatography using AcOEt/MeOH (100:0 to 80:20) as eluent.

(–)-(*S*,*E*)-*N*,*N*-Dimethyl-4-phenylbut-3-en-2-amine, **IV-9a**.

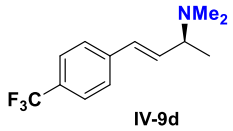


From (*S*,*E*)-4-phenylbut-3-en-2-yl acetate (834 mg, 4.4 mmol), following the general procedure described above, compound **IV-9a** (555 mg, 3.2 mmol) was obtained in 72% yield as a pale yellow oil after flash column chromatography (AcOEt/MeOH, 70/30).

^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.42-7.22 (m, 5H), 6.46 (d, *J* = 16.0 Hz, 1H), 6.22 (dd, *J* = 16.0, 8.0 Hz, 1H), 3.05 (quint, *J* = 6.8 Hz, 1H), 2.32 (s, 6H), 1.26 (d, *J* = 6.5 Hz, 3H). **^{13}C-NMR** (75 MHz, $CDCl_3$): δ 137.2, 132.3, 130.7, 128.6, 127.3, 126.3, 62.9, 42.2, 18.1. **HRMS-ESI$^+$** m/z calculated for $C_{12}H_{18}N$ **[M+H]$^+$:** 176.1433, found 176.1440.

Compound **IV-9a** was obtained in 96:4 enantiomeric ratio determined by chiral GC-MS using CP-Chirasil Dex CB (60→110 °C @ 10 °C/min, hold 2 min, then →130 °C @ 1 °C/min, then →180 °C @ 10 °C/min; flow rate 1.0 mL/min.). τ_{major} = 22.0 min, τ_{minor} = 21.9 min. **$[\alpha]^{20}_D$** = –60.5 (*c* = 1.0, $CHCl_3$).

(–)-(*S*,*E*)-*N*,*N*-Dimethyl-4-(4-(trifluoromethyl)phenyl)but-3-en-2-amine, **IV-9d**.

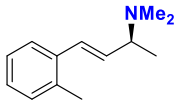


IV-9d

From (*S*,*E*)-4-(4-(trifluoromethyl)phenyl)but-3-en-2-yl acetate (0.8 g, 3.29 mmol), following the general procedure described above, compound **IV-9d** (707 mg, 2.9 mmol) was obtained in 89% yield as a pale yellow oil after flash column chromatography (AcOEt/MeOH, 70/30).

^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.53 (d, *J* = 8.3 Hz, 2H), 7.45 (d, *J* = 8.3 Hz, 2H), 6.52 (d, *J* = 116.5 Hz, 1H), 6.30 (dd, *J* = 15.9, 7.5 Hz, 1H), 3.26-3.17 (m, 1H), 2.33 (s, 6H), 1.28 (d, *J* = 6.7 Hz, 3H). **^{13}C-NMR** (75 MHz, $CDCl_3$): δ 140.8, 135.4, 129.5, 129.3 (q, J_{C-F} = 32.0 Hz), 126.5, 125.6 (q, J_{C-F} = 4.3 Hz), 124.4 (q, J_{C-F} = 272.2 Hz), 62.84, 42.31, 17.81. **HRMS-ESI$^+$** m/z calculated for $C_{13}H_{17}NF_3$ **$[M+H]^+$:** 244.1307, found 244.1315. **$[\alpha]^{20}_D$**= –135.7 (*c* = 1.0, $CHCl_3$).

(–)-(*S*,*E*)-*N*,*N*-Dimethyl-4-(*o*-tolyl)but-3-en-2-amine, **IV-9f**.



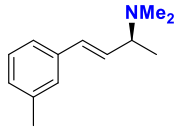
IV-9f

From (*S*,*E*)-4-(*o*-tolyl)but-3-en-2-yl acetate (0.9 g, 4.50 mmol), following the general procedure described above, compound **IV-9f** (596 mg, 3.2 mmol) was obtained in 70% yield as a pale yellow oil after flash column chromatography (AcOEt/MeOH, 70/30).

^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.45-7.42 (m, 1H), 7.18-7.11 (m, 3H), 6.65 (d, *J* = 15.6 Hz, 1H), 6.06 (dd, *J* = 15.8, 8.0 Hz, 1H), 3.11-3.02 (quint, *J* = 7.1 Hz, 1H), 2.35 (s, 3H), 2.31 (s, 6H), 1.26 (d, *J* = 6.7 Hz, 3H). **^{13}C-NMR** (75 MHz, $CDCl_3$): δ 136.5, 135.4, 133.5, 130.4, 129.0, 127.4, 126.2, 125.9, 63.3, 42.3, 31.1, 20.0, 18.5. **HRMS-EI^{+}** m/z calculated for $C_{13}H_{19}N$ **[M]$^{+}$:** 189.1517, found 189.1514.

Compound **IV-9f** was obtained in 97:3 enantiomeric ratio determined by GC-MS using CP-Chirasil Dex CB. τ_{major} = 29.0 min, τ_{minor} = 28.8 min. **[α]$^{20}_{D}$=** –35.1 (*c* = 1.0, $CHCl_3$).

(–)-(*S*,*E*)-*N*,*N*-Dimethyl-4-(*m*-tolyl)but-3-en-2-amine, **IV-9g.**



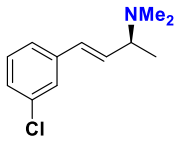
IV-9g

From (*S*,*E*)-4-(*m*-tolyl)but-3-en-2-yl acetate (0.4 g, 2.1 mmol), following the general procedure described above, compound **IV-9g** (167 mg, 0.9 mmol) was obtained in 41% yield as a pale yellow oil after flash column chromatography (AcOEt/MeOH, 70/30).

^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.14 (m, 4H), 6.44 (d, *J* = 15.9 Hz, 1H), 6.22 (dd, *J* = 15.9 Hz, 7.8 Hz, 1H), 3.04 (m, 1H), 2.36 (s, 3H), 2.30 (s, 6H), 1.25 (d, *J* = 6.2 Hz, 3H). **^{13}C-NMR** (75 MHz, $CDCl_3$) δ 138.2, 137.1, 131.5, 131.3, 128.6, 128.3, 127.1, 123.6, 63.1, 42.1, 21.5, 18.1. **HRMS-EI^{+}** m/z calculated for $C_{13}H_{19}N$ **[M]$^{+}$:** 189.1517, found 189.1512.

Compound **IV-9g** was obtained in 97:3 enantiomeric ratio determined by GC-MS using CP-Chirasil Dex CB (60→110 °C @ 10 °C/min, hold 2 min, then →130 °C @ 1 °C/min, then →180 °C @ 10 °C/min; flow rate 1.0 mL/min.). τ_{major} = 31.2 min, τ_{minor} = 31.0 min. **[α]$^{20}_{D}$** = –51.2 (*c* = 1.0, $CHCl_3$).

(–)-(*S*,*E*)-4-(3-Chlorophenyl)-*N*,*N*-dimethylbut-3-en-2-amine, **IV-9i**.

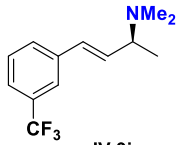


IV-9i

From (*S*,*E*)-4-(3-chlorophenyl)but-3-en-2-yl acetate (0.3 g, 1.3 mmol), following the general procedure described above, compound **IV-9i** (136 mg, 0.7 mmol) was obtained in 49% yield as a pale yellow oil after flash column chromatography (AcOEt/MeOH, 70/30).

^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.39 (s broad, 1H), 7.32-7.20 (m, 3H), 6.45 (d, *J* = 16.0 Hz, 1H), 6.26 (dd, *J* = 16.1, 8.2 Hz, 1H), 3.09 (quint, *J* = 7.0 Hz, 1H), 2.33 (s, 6H), 1.27 (d, *J* = 6.5 Hz, 3H). **^{13}C-NMR** (75 MHz, $CDCl_3$): δ 139.0, 134.4, 133.7, 129.7, 129.4, 127,2, 126.2, 124.4, 62.6, 42.0, 17.7. **HRMS-ESI^{+}** m/z calculated for $C_{12}H_{17}NCl$ **[M+H]$^{+}$:** 210.1044, found 210.1049. **[α]$^{20}_{D}$=** –41.3 (*c* = 1.0, $CHCl_3$).

(–)-(*S*,*E*)-*N*,*N*-Dimethyl-4-(3-(trifluoromethyl)phenyl)but-3-en-2-amine, **IV-9j**.



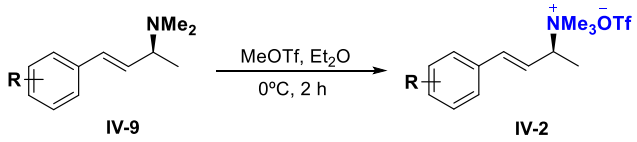
IV-9j

From (*S*,*E*)-4-(3-(trifluoromethyl)phenyl)but-3-en-2-yl acetate (2.2 g, 8.3 mmol), following the general procedure described above, compound **IV-9j** (1.3 g, 5.2 mmol) was obtained in 62% yield as a pale yellow oil after flash column chromatography (AcOEt/MeOH, 70/30).

^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.60 (s, 1H), 7.54 (d, *J* = 7.4 Hz, 1H), 7.44 (m, 2H), 6.50 (d, *J* = 16.0 Hz, 1H), 6.28 (dd, *J* = 16.0, 7.8 Hz, 1H), 3.10 (quint, *J* = 7.0, 6.6 Hz, 1H), 2.31 (s, 6H), 1.26 (d, *J* = 6.6 Hz, 3H).**^{13}C-NMR** (75 MHz, $CDCl_3$) δ 138.0, 134.1, 131.2 (q, $J_{C\text{-}F}$ = 31.6 Hz), 129.8, 129.5 (q, $J_{C\text{-}F}$ = 1.2 Hz), 129.2, 124.3 (q, $J_{C\text{-}F}$ = 271.3 Hz), 124.1(q, $J_{C\text{-}F}$ = 3.7 Hz), 123.2 (q, $J_{C\text{-}F}$ = 3.7 Hz), 62.8, 42.1, 17.8. **HRMS-ESI^{+}** m/z calculated for $C_{13}H_{17}NF_3$ **[M+H]$^{+}$:** 244.1307, found 244.1312.

Compound **IV-9j** was obtained in 99:1 enantiomeric ratio determined by GC-MS using CP-Chirasil Dex CB (60→110 °C @ 10 °C/min, hold 2 min, then →130 °C @ 1 °C/min, then →180 °C @ 10 °C/min; flow rate 1.0 mL/min.). τ_{major} = 25.0 min, τ_{minor} = 24.7 min. **$[\alpha]^{20}_{D}$** = –77.4 (*c* = 1.0, $CHCl_3$).

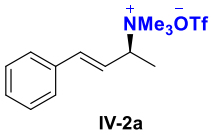
4.5.1.7. Synthesis of allylic ammonium salts **IV-2**.



IV-9 **IV-2**

To a solution of the allylic amine (1 equiv) in Et_2O (2 mL/mmol of amine) was added methyl trifluoromethanesulfonate (1.1 equiv) dropwise at 0 ºC. The reaction mixture was stirred at 0 ºC for 30 minutes. The crude was concentrated under reduced pressure and purified by flash column chromatography using AcOEt/MeOH (from 90:10 to 50:50) as eluent.

(–)-(*S*,*E*)-*N*,*N*,*N*-Trimethyl-4-phenylbut-3-en-2-aminium trifluoromethanesulfonate, **IV-2a**.

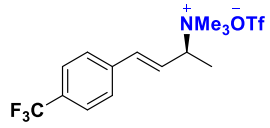


IV-2a

From (*S*,*E*)-*N*,*N*-dimethyl-4-phenylbut-3-en-2-amine (1.1 g, 6.27 mmol), following the general procedure described above, compound **IV-2a** (2.0 g, 5.96 mmol) was obtained in 95% yield as a white solid.

^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.44 (m, 2H), 7.34 (m, 3H), 6.99 (d, *J* = 15.5 Hz, 1H), 6.09 (dd, *J* = 15.4, 9.2 Hz, 1H), 4.37 (quint, *J* = 6.9 Hz, 1H), 3.14 (s, 9H), 1.59 (d, *J* = 6.6 Hz, 3H). **^{13}C-NMR** (75 MHz, $CDCl_3$): δ 140.8, 134.6, 129.5, 128.9, 127.3, 123.0 [q, $J_{C\text{-}F}$ = 318.0 Hz], 120.0, 73.2, 50.8, 15.3. **HRMS-ESI$^+$** m/z calculated for $C_{13}H_{20}N$ **[M–OTf]$^+$:** 190.1590, found 190.1590. **[α]$^{20}_D$** = –53.6 (*c* = 1.0, $CHCl_3$).

(–)-(*S*,*E*)-*N*,*N*,*N*-Trimethyl-4-(4-(trifluoromethyl)phenyl)but-3-en-2-aminium trifluoromethanesulfonate, **IV-2d**.

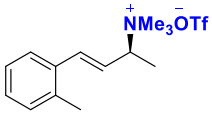


IV-2d

From (*S*,*E*)-*N*,*N*-dimethyl-4-(4-(trifluoromethyl)phenyl)but-3-en-2-amine (0.4 g, 1.64 mmol), following the general procedure described above, compound **IV-2d** (0.6 g, 1.54 mmol) was obtained in 93% yield as a colorless oil after flash column chromatography (AcOEt/MeOH from 90:10 to 50:50).

^{1}H-NMR (300 MHz, Acetone-d_6): δ 7.77 (d, *J* = 8.1 Hz, 2H), 7.65 (d, *J* = 8.1 Hz, 2H), 7.14 (d, *J* = 16.0 Hz, 1H), 6.71 (dd, *J* = 15.7, 9.4 Hz, 1H), 4.52 (m, 1H), 3.25 (s, 9H), 2.23 (s, 3H), 1.64 (m, 3H). **^{13}C-NMR** (75 MHz, Acetone-d_6): δ 140.2, 138.4, 130.7 (q, $J_{C\text{-}F}$ = 32.3 Hz), 128.7, 126.9 (q, $J_{C\text{-}F}$ = 269.9 Hz), 126.6 (q, $J_{C\text{-}F}$ = 3.8 Hz), 125.8, 123.9 (q, $J_{C\text{-}F}$ = 320.7 Hz), 73.4, 51.3, 15.5. **HRMS-ESI$^+$** m/z calculated for $C_{14}H_{19}NF_3$ **[M–OTf]$^+$:** 258.1464, found 258.1471. **[α]$^{20}_D$** = –171.2 (*c* = 1.0, $CHCl_3$).

(–)-(*S*,*E*)-*N*,*N*,*N*-Trimethyl-4-(*o*-tolyl)but-3-en-2-aminium trifluoromethanesulfonate, **IV-2f**.

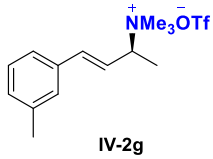


IV-2f

From (*S*,*E*)-*N*,*N*-dimethyl-4-(*o*-tolyl)but-3-en-2-amine (0.6 g, 3.17 mmol), following the general procedure described above, compound **IV-2f** (0.5 g, 1.52 mmol) was obtained in 48% yield as a colorless oil after flash column chromatography (AcOEt/MeOH from 90:10 to 50:50).

^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.38 (m, 1H), 7.19-7.07 (m, 4H), 5.89 (dd, *J* = 15.3, 9.5 Hz, 1H), 4.34 (m, 1H), 3.07 (s, 9H), 2.28 (s, 3H), 1.50 (d, *J* = 6.4 Hz, 3H). **^{13}C-NMR** (75 MHz, $CDCl_3$): δ 139.2, 136.7, 133.8, 130.8, 129.5, 126.5, 126.1, 122.9 (q, $J_{C\text{-}F}$ = 321.5 Hz), 121.2, 73.5, 51.0, 19.6, 15.2. **HRMS-ESI$^+$** m/z calculated for $C_{14}H_{22}N$ **[M–OTf]$^+$:** 204.1746, found 204.1743. **[α]$^{20}_D$** = –75.8 (*c* = 1.0, $CHCl_3$).

(–)-(*S*,*E*)-*N*,*N*,*N*-Trimethyl-4-(m-tolyl)but-3-en-2-aminium trifluoromethanesulfonate, **IV-2g**.



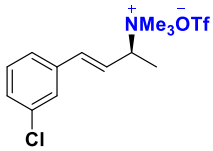
IV-2g

From (*S*,*E*)-*N*,*N*-dimethyl-4-(*m*-tolyl)but-3-en-2-amine (0.25 g, 1.34 mmol), following the general procedure described above, compound **IV-2g** (0.4 g, 1.1 mmol) was obtained in 84% yield as a colorless oil after flash column chromatography (AcOEt/MeOH from 90:10 to 50:50).

^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.14 (m, 3H), 7.03 (m, 1H), 6.83 (d, *J* = 15.7 Hz, 1H), 6.02 (dd, *J* = 15.5, 9.4 Hz, 1H), 4.23 (quint, *J* = 6.6 Hz, 1H), 3.00 (s, 9H), 2.23 (s, 3H), 1.47 (d, *J* = 6.5 Hz, 3H). **^{13}C-NMR** (75 MHz, $CDCl_3$): δ 140.8, 138.5, 134.5, 130.1, 128.7, 127.7, 124.5, 122.8 (q, $J_{C\text{-}F}$ =

320.1 Hz),119.8, 73.2, 50.6, 21.1, 15.1. **HRMS-ESI**$^{+}$ m/z calculated for $C_{14}H_{22}N$ **[M–OTf]**$^{+}$**:** 204.1746, found 204.1745. **[α]**$^{20}_{D}$ = –12.3 (*c* = 1.0, $CHCl_3$).

(–)-(*S*,*E*)-4-(3-Chlorophenyl)-*N*,*N*,*N*-trimethylbut-3-en-2-aminium trifluoromethanesulfonate, **IV-2i**.

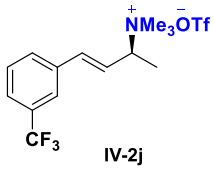


IV-2i

From (*S*,*E*)-4-(3-chlorophenyl)-*N*,*N*-dimethylbut-3-en-2-amine (0.6 g, 2.76 mmol), following the general procedure described above, compound **IV-2i** (0.93 g, 2.5 mmol) was obtained in 90% yield as a colorless oil after flash column chromatography (AcOEt/MeOH from 90:10 to 50:50).

^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.35 (s broad, 1H), 7.28 (m, 1H), 7.19 (m, 2H), 6.83 (d, *J* = 15.8 Hz, 1H), 6.06 (dd, *J* = 15.5, 9.5 Hz, 1H), 4.32 (quint, *J* = 6.8 Hz, 1H), 3.06 (s, 9H), 1.51 (d, *J* = 6.7 Hz, 3H). **^{13}C-NMR** (75 MHz, $CDCl_3$): δ 139.6, 136.5, 134.8, 130.3, 129.4, 127.1, 125.7, 122.9 (q, $J_{C\text{-}F}$ = 320.7 Hz),121.5, 73.0, 50.9, 15.3. **HRMS-ESI**$^{+}$ m/z calculated for $C_{13}H_{19}NCl$ **[M–OTf]**$^{+}$**:** 224.1200, found 224.1197. **[α]**$^{20}_{D}$ = –67.8 (*c* = 1.0, $CHCl_3$).

(–)-(*S*,*E*)-4-(3-(Trifluoromethyl)phenyl)-*N*,*N*,*N*-trimethylbut-3-en-2-aminium trifluoromethanesulfonate, **IV-2j**.



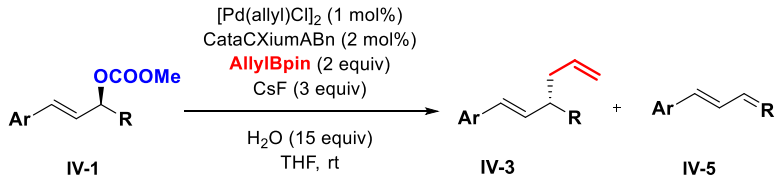
IV-2j

From (*S*,*E*)-4-(3-chlorophenyl)-*N*,*N*-dimethylbut-3-en-2-amine (0.75 g, 3.08 mmol), following the general procedure described above, compound **IV-2j** (0.53 g, 1.3 mmol) was obtained in

42% yield as a colorless oil after flash column chromatography (AcOEt/MeOH from 90:10 to 50:50).

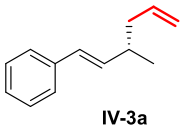
^{1}H-NMR (300 MHz, $(CD_3)_2CO$): δ 7.86 (m, 2H), 7.69 – 7.55 (m, 2H), 7.14 (d, *J* = 15.8 Hz, 1H), 6.73 (dd, *J* = 15.8, 9.4 Hz, 1H), 4.54 (m, 1H), 3.30 (s, 9H), 1.74 – 1.64 (m, 3H). **^{13}C-NMR** (75 MHz, $CDCl_3$): δ 138.6, 137.6, 132.0, 131.4 (q, $J_{C\text{-}F}$ = 28.0 Hz), 130.56, 129.1 (q, $J_{C\text{-}F}$ = 316.7 Hz), 126.1 (q, $J_{C\text{-}F}$ = 4.3 Hz), 125.1, 124.5 (q, $J_{C\text{-}F}$ = 4.3 Hz), 121.7 (q, $J_{C\text{-}F}$ = 252.5 Hz), 73.8, 51.59, 51.53, 51.48, 15.6. **HRMS-ESI^{+}** m/z calculated for $C_{14}H_{19}NF_3$ **[M−OTf]$^{+}$:** 258.1464, found 258.1469. **$[\alpha]^{20}_{D}$**= –89.2(*c* = 1.0, $CHCl_3$).

4.5.2. Palladium-catalyzed allyl-allyl cross-coupling reaction of allylic carbonates.



In a 1 dram vial provided with a PTFE septa cap were weighted $[Pd(allyl)Cl]_2$ (0.7 mg, 0.002 mmol, 1 mol%) and the ligand di(1-adamantyl)benzylphosphine (CataCXiumABn) (1.6 mg, 0.004 mmol, 2 mol%). The vial was introduced to a glove box under nitrogen atmosphere and THF (0.2 mL) was added. The mixture was stirred 10 minutes at rt. To this solution, the allylic carbonate (0.2 mmol) in THF (1.2 mL) was added and then, the allyl pinacol boronic ester (2 equiv), CsF (3 equiv) were added subsequently. Finally, the vial was taken out of the glove box and H_2O (15 equiv) was added. The reaction mixture was stirred overnight at rt. The reaction was filtered through a short pad of celite and rinsed with DCM. The solvent was evaporated under reduced pressure and the crude product purified by flash column chromatography using hexane as eluent. The ratio of **IV-3** and **IV-5** was determined by ^{1}H-RMN. Yields are corrected based on the amount of elimination product isolated with the desired product.

(+)-(*S*,*E*)-(3-Methylhexa-1,5-dien-1-yl)benzene, **IV-3a**.


IV-3a

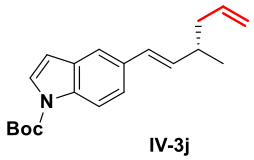
From (*S*,*E*)-methyl (4-phenylbut-3-en-2-yl) carbonate (41 mg, 0.2 mmol) following the general procedure described above, compound **IV-3a** (30 mg,

0.17 mmol) was obtained in 87% yield as a colorless oil after flash column chromatography in hexane along with 8% of elimination product.

^{1}H-RMN (300 MHz, $CDCl_3$): δ 7.42-7.22 (m, 5H), 6.39 (d, *J* = 15.5 Hz, 1H), 6.22 (dd, *J* = 16.1, 7.4 Hz, 1H), 5.86 (m, 1H), 5.08 (m, 2H), 2.46 (quint, *J* = 6.6 Hz, 1H), 2.22 (m, 2H), 1.16 (t, *J* = 6.8 Hz, 3H). **^{13}C-RMN** (300 MHz, $CDCl_3$): δ 137.9, 137.1, 136.2, 128.6, 128.3, 127.0, 126.1, 116.1, 41.4, 37.0, 20.0.

Compound **IV-3a** was obtained in 98:2 enantiomeric ratio determined by chiral GC-MS on a Chirasil Dex-CB column (60→110 °C @ 10 °C/min, hold 2 min, then →130 °C @ 1 °C/min, then →180 °C @ 10 °C/min; flow rate 1.0 mL/min.). τ_{major} = 21.7 min, τ_{minor} = 22.1 min. **$[\alpha]^{20}_{D}$ =** +44.5 (*c* = 1.0, $CHCl_3$). The absolute configuration was stablished by comparison with the previously reported compound.[21]

(+)-(*S*,*E*)-*tert*-Butyl-5-(3-methylhexa-1,5-dien-1-yl)-1H-indole-1-carboxylate, **IV-3b**.



IV-3j

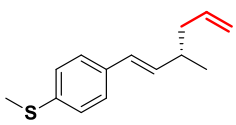
From *tert*-butyl-(*E*)-5-(3-((methoxycarbonyl) oxy)but-1-en-1-yl)-1H-indole-1-carboxylate (69.1 mg, 0.2 mmol), following the general procedure described above, compound **IV-3b** (58 mg, 0.19 mmol) was obtained in 93% yield as a colorless oil after flash column chromatography in hexane.

^{1}H-RMN (300 MHz, $CDCl_3$): δ 8.09 (d, *J* = 8.2 Hz, 1H), 7.59 (d, *J* = 3.3 Hz, 1H), 7.53 (s broad, 1H), 7.39 (d, *J* = 8.5 Hz, 1H), 6.55 (d, *J* = 3.5 Hz, 1H), 6.50 (d, *J* = 15.8 Hz, 1H), 6.19 (dd, *J* = 15.7, 7.3 Hz, 1H), 5.88 (m, 1H), 5.03 (m, 2H), 2.45 (quint, *J* = 6.8 Hz, 1H), 2.21 (m, 2H), 1.70 (s, 9H), 1.15 (t, *J* = 6.8 Hz, 3H). **^{13}C-RMN** (300 MHz, $CDCl_3$): δ 149.9, 137.3,

135.0, 134.6, 132.9, 131.1, 128.6, 126.4, 122.7, 118.5, 116.1, 115.2, 107.5, 83.8, 41.7, 37.1, 28.4, 20.2. **HRMS-ESI**$^{+}$ m/z calculated for $C_{20}H_{25}NO_2Na$ **[M+Na]**$^{+}$**:** 334.1777, found 334.1792. **[α]**$^{20}_{D}$= +14.4 (*c* = 1.0, $CHCl_3$).

Compound **IV-3b** was derivatized into the corresponding *tert*-butyl (*S*,*E*)-5-(6-hydroxy-3-methylhex-1-en-1-yl)-1H-indole-1-carboxylate to determinate its enantiomeric ratio (See compound **IV-11b**).

(+)-(*S*,*E*)-Methyl(4-(3-methylhexa-1,5-dien-1-yl)phenyl)sulfane, **IV-3c**.



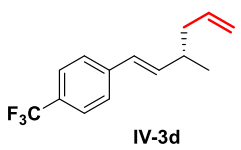
IV-3c

From (*S*,*E*)-methyl(4-(4-(methylthio)phenyl) but-3-en-2-yl) carbonate (52.9 mg, 0.2 mmol), following the general procedure described above, compound **IV-3c** (40 mg, 0.18 mmol) was obtained in 91% yield as a colorless oil after flash column chromatography in hexane along with 7% of elimination product.

^{1}H-RMN (300 MHz, $CDCl_3$): δ 7.19 (d, *J* = 8.4 Hz, 2H), 7.11 (d, *J* = 8.5 Hz, 2H), 6.23 (d, *J* = 15.9 Hz, 1H), 6.03 (dd, *J* = 15.9, 7.3 Hz, 1H), 5.80 – 5.61 (m, 1H), 5.02 – 4.88 (m, 2H), 2.39 (s, 3H), 2.31 (m, 1H), 2.18 – 1.98 (m, 2H), 1.01 (d, *J* = 6.7 Hz, 3H). **^{13}C-RMN** (300 MHz, $CDCl_3$): δ 137.0, 136.8, 135.8, 135.1, 127.7, 127.1, 126.6, 116.1, 41.5, 37.0, 20.0, 16.3. **HRMS-EI**$^{+}$ m/z calculated for $C_{14}H_{19}S$ **[M]**$^{+}$**:** 219.1207, found 219.1186.

Compound **IV-3c** was obtained in 95:5 enantiomeric ratio determined by HPLC using Chiralpak-IG column [Hexane/iPrOH (100:0 to 99.5:0.5 in 30 min)], 0.5 mL/min, τ_{major} = 14.2 min, τ_{minor} = 15.87 min. **[α]**$^{20}_{D}$ = +22.1 (*c* = 1.0, $CHCl_3$).

(+)-(*S*,*E*)-1-(3-Methylhexa-1,5-dien-1-yl)-4-(trifluoromethyl)benzene, **IV-3d**.



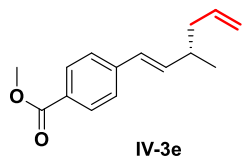
IV-3d

From (*S*,*E*)-4-(4-trifluorophenyl)but-3-en-2-yl methyl carbonate (54.8 mg, 0.2 mmol), following the general procedure described above, compound **IV-3d** (28 mg, 0.12 mmol) was obtained in 58% yield after flash column chromatography in hexane along with 9% of elimination product.

^{1}H-RMN (300 MHz, $CDCl_3$): δ 7.54 (d, *J* = 8.2 Hz, 2H), 7.43 (d, *J* = 8.2 Hz, 2H), 6.39 (d, *J* = 16.0 Hz, 1H), 6.25 (dd, *J* = 15.9, 7.2 Hz, 1H), 5.80 (m, 1H), 5.13 – 4.97 (m, 2H), 2.44 (hept, *J* = 6.9 Hz, 1H), 2.29 – 2.07 (m, 2H), 1.12 (d, *J* = 6.7 Hz, 3H). **^{13}C-RMN** (300 MHz, $CDCl_3$): 141.5, 139.0, 136.8, 128.8 (q, $J_{C\text{-}F}$ = 32.5 Hz), 127.2, 126.3, 125.6 (q, $J_{C\text{-}F}$ = 3.8 Hz), 124.4 (q, $J_{C\text{-}F}$ = 272 Hz), 116.4, 41.3, 37.1, 19.9. **HRMS-EI^{+}** m/z calculated for $C_{14}H_{15}F_3$ **[M]$^{+}$:** 240.1126, found 240.1117.

Compound **IV-3d** was obtained in 97:3 enantiomeric ratio determined by chiral GC-MS using CP-Chirasil Dex CB column (60→110 °C @ 10 °C/min, hold 2 min, then →130 °C @ 1 °C/min, then →180 °C @ 10 °C/min; flow rate 1.0 mL/min.). τ_{major} = 22.3 min, τ_{minor} = 22.2 min. **$[\alpha]^{20}_{D}$** = +1.5 (*c* = 1.0, $CHCl_3$).

(+)-Methyl (*S*,*E*)-4-(3-methylhexa-1,5-dien-1-yl)benzoate, **IV-3e**.



IV-3e

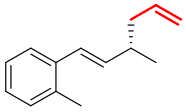
From methyl (*S*,*E*)-4-(3-((methoxycarbonyl) oxy)but-1-en-1-yl)benzoate (52.9 mg, 0.2 mmol), following the general procedure described above, compound **IV-3e** (33 mg, 0.14 mmol) was obtained

in 72% yield as a colorless oil after flash column chromatography in hexane along with 11% of elimination product.

^{1}H-RMN (300 MHz, $CDCl_3$): δ 7.88 (d, *J* = 8.4 Hz, 2H), 7.31 (d, *J* = 8.3 Hz, 2H), 6.32 (d, *J* = 16.0 Hz, 1H), 6.20 (dd, *J* = 15.9, 7.1 Hz, 1H), 5.72 (m, 1H), 5.06 – 4.84 (m, 2H), 3.82 (s, 3H), 2.35 (hept, *J* = 6.7 Hz, 1H), 2.20 – 1.97 (m, 2H), 1.03 (d, *J* = 6.7 Hz, 3H).**^{13}C-RMN** (300 MHz, $CDCl_3$): δ 167.1, 142.5, 139.1, 136.8, 130.0, 128.5, 127.7, 126.0, 116.4, 52.1, 41.3, 37.2, 19.9. **HRMS-GCEI^{+}** m/z calculated for $C_{15}H_{19}O_2$ **[M]$^{+}$:** 231.1385, found 231.1376.

Compound **IV-3e** was obtained in 98:2 enantiomeric ratio determined by HPLC using Chiralpak-IG column [Hexane/iPrOH (99.7:0.3)], 0.5 mL/min, τ_{major} = 20.1 min, τ_{minor} = 19.8 min. **$[\alpha]^{20}_{D}$** = +40.7 (*c* = 1.0, $CHCl_3$).

(+)-(*S*,*E*)-1-Methyl-2-(3-methylhexa-1,5-dien-1-yl)benzene, **IV-3f**.



IV-3f

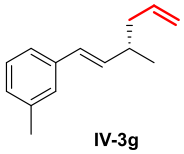
From (*S*,*E*)-methyl (4-(*o*-tolyl)but-3-en-2-yl) carbonate (44.1 mg, 0.2 mmol), following the general procedure described above, compound **IV-3f** (36 mg, 0.19 mmol) was obtained in 97% yield as a colorless oil after flash column chromatography in hexane.

^{1}H-RMN (300 MHz, $CDCl_3$): δ 7.39 (d, *J* = 6.3 Hz, 1H), 7.13 (m, 3H), 6.52 (d, *J* = 15.5 Hz, 1H), 5.99 (dd, *J* = 15.6, 7.4 Hz, 1H), 5.82 (m, 1H), 5.04 (m, 2H), 2.43 (quint, *J* = 6.7 Hz, 1H), 2.33 (s, 3H), 2.19 (m, 2H), 1.10 (t, *J* = 6.8 Hz, 3H). **^{13}C-RMN** (300 MHz, $CDCl_3$): δ 137.6, 137.1, 135.1, 130.2, 126.9, 126.2, 126.1, 125.6, 116.0, 41.6, 37.3, 20.2, 19.9. **HRMS-EI^{+}** m/z calculated for $C_{14}H_{18}$ **[M]$^{+}$:** 186.1409, found 186.1412.

Compound **IV-3f** was obtained in 99:1 enantiomeric ratio determined by chiral GC-MS using CP-Chirasil Dex CB (60→110 °C @ 10 °C/min,

hold 2 min, then →130 °C @ 1 °C/min, then →180 °C @ 10 °C/min; flow rate 1.0 mL/min.). τ_{major} = 25.4 min, τ_{minor} = 25.3 min. **[α]$^{20}_{D}$** = +28.4 (*c* = 1.0, $CHCl_3$).

(+)-(*S*,*E*)-1-Methyl-3-(3-methylhexa-1,5-dien-1-yl)benzene, **IV-3g**.

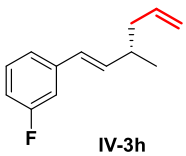

IV-3g

From (*S*,*E*)-methyl (4-(m-tolyl)but-3-en-2-yl) carbonate (44.1 mg, 0.2 mmol), following the general procedure described above, compound **IV-3g** (34 mg, 0.18 mmol) was obtained in 91% yield as a colorless oil after flash column chromatography in hexane along with 6% of elimination product.

^{1}H-RMN (300 MHz, $CDCl_3$): δ 7.15-7.05 (m, 3H), 6.94 (s broad, 1H), 6.28 (d, *J* = 15.5 Hz, 1H), 6.04 (dd, *J* = 15.9, 7.4 Hz, 1H), 5.72 (m, 1H), 4.95 (m, 2H), 2.31 (quint, *J* = 6.7 Hz, 1H), 2.25 (s, 3H), 2.06 (m, 2H), 1.02 (t, *J* = 6.7 Hz, 3H). **^{13}C-RMN** (300 MHz, $CDCl_3$): δ 138.1, 137.9, 137.1, 136.0, 128.5, 128.4, 127.8, 126.8, 123.3, 116.0, 41.5, 37.0, 21.5, 20.1. **HRMS-EI^{+}** m/z calculated for $C_{14}H_{18}$ **[M]$^{+}$:** 186.1409, found 186.1407.

Compound **IV-3g** was obtained in 97:3 enantiomeric ratio determined by chiral GC-MS on a Chirasil Dex-CB column (60→110 °C @ 10 °C/min, hold 2 min, then →130 °C @ 1 °C/min, then →180 °C @ 10 °C/min; flow rate 1.0 mL/min.). τ_{major} = 25.1 min, τ_{minor} = 25.0 min. **[α]$^{20}_{D}$** = +27.6 (*c* = 1.0, $CHCl_3$).

(+)-(*S*,*E*)-1-Fluoro-3-(3-methylhexa-1,5-dien-1-yl)benzene, **IV-3h**.



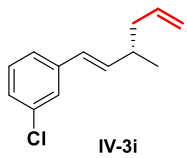
IV-3h

From (*S*,*E*)-4-(3-fluorophenyl)but-3-en-2-yl methyl carbonate (45.0 mg, 0.2 mmol), following the general procedure described above, compound **IV-3h** (27 mg, 0.14 mmol) was obtained in 70% yield as a colorless oil after flash column chromatography in hexane along with 10% of elimination product.

^{1}H-RMN (300 MHz, $CDCl_3$): δ 7.30 – 7.18 (m, 1H), 7.14 – 6.99 (m, 2H), 6.88 (td, *J* = 8.7, 2.5 Hz, 1H), 6.33 (d, *J* = 15.9 Hz, 1H), 6.16 (dd, *J* = 15.9, 7.3 Hz, 1H), 5.80 (m, 1H), 5.13 – 4.95 (m, 2H), 2.51 – 2.31 (m, 1H), 2.29 – 2.04 (m, 2H), 1.10 (d, *J* = 6.7 Hz, 3H). **^{13}C-RMN** (300 MHz, $CDCl_3$): δ 163.3 (d, $J_{C\text{-}F}$ = 245 Hz), 140.4 (d, $J_{C\text{-}F}$ = 7.8 Hz), 137.3 (d, $J_{C\text{-}F}$ = 57 Hz), 130.0 (d, $J_{C\text{-}F}$ = 8.1 Hz), 127.4 (d, $J_{C\text{-}F}$ = 3.7 Hz), 122.1 (d, $J_{C\text{-}F}$ = 3.7 Hz), 116.3, 113.8 (d, $J_{C\text{-}F}$ = 21.5 Hz), 112.6 (d, $J_{C\text{-}F}$ = 21.5 Hz), 41.4, 37.0, 19.9. **HRMS-GCEI^{+}** m/z calculated for $C_{13}H_{16}F$ **[M]$^{+}$:** 191.1236, found 191.1195.

Compound **IV-3h** was obtained in 98:2 enantiomeric ratio determined by chiral GC-MS using CP-Chirasil Dex CB (60→110 °C @ 10 °C/min, then →140°C @ 1 °C/min, then →180 °C @ 20 °C/min; flow rate 1.0 mL/min.). τ_{major} = 20.6 min, τ_{minor} = 20.4 min. **$[\alpha]^{20}_{D}$** = +13.3 (*c* = 1.0, $CHCl_3$).

(+)-(*S*,*E*)-1-Chloro-3-(3-methylhexa-1,5-dien-1-yl)benzene, **IV-3i**.



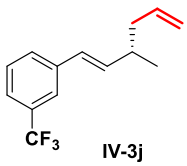
IV-3i

From (*S*,*E*)-4-(3-chlorophenyl)but-3-en-2-yl methyl carbonate (48.1 mg, 0.2 mmol), following the general procedure described above, compound **IV-3i** (28 mg, 0.14 mmol) was obtained in 68% yield as a colorless oil after flash column chromatography in hexane along with 19% of elimination product.

^{1}H-RMN (300 MHz, $CDCl_3$): δ 7.25 (s broad, 1H), 7.14-7.06 (m, 3H), 6.19 (d, *J* = 15.9 Hz, 1H), 6.06 (dd, *J* = 15.9, 7.2 Hz, 1H), 5.71 (m, 1H), 4.96 (m, 2H), 2.32 (quint, *J* = 6.6 Hz, 1H), 2.07 (m, 2H), 1.01 (t, *J* = 6.7 Hz, 3H). **^{13}C-RMN** (300 MHz, $CDCl_3$): δ 139.8, 137.7, 136.8, 134.5, 129.8, 127.1, 126.9, 126.0, 124.3, 116.3, 41.3, 37.0, 19.9. **HRMS-EI^{+}** m/z calculated for $C_{13}H_{15}Cl$ **[M]$^{+}$:** 206.0862, found 206.0867.

Compound **IV-3i** was obtained in 99:1 enantiomeric ratio determined by chiral GC-MS on a Chirasil Dex-CB column (60→110 °C @ 10 °C/min, hold 2 min, then →130 °C @ 1 °C/min, then →180 °C @ 10 °C/min; flow rate 1.0 mL/min.). τ_{major} = 33.1 min, τ_{minor} = 33.3 min. **$[\alpha]^{20}_{D}$** = +24.1 (*c* = 1.0, $CHCl_3$).

(+)-(*S*,*E*)-1-(3-Methylhexa-1,5-dien-1-yl)-3-(trifluoromethyl)benzene, **IV-3j**.



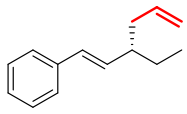
IV-3j

From (*S*,*E*)-methyl (4-(3-(trifluoromethyl)phenyl)but-3-en-2-yl) carbonate (54.8 mg, 0.2 mmol), following the general procedure described above, compound **IV-3j** (36 mg, 0.15 mmol) was obtained in 75% yield as a colorless oil after flash column chromatography in hexane along with 25% of elimination product.

^{1}H-RMN (300 MHz, $CDCl_3$): δ 7.59 (s broad, 1H), 7.52-7.37 (m, 3H), 6.37 (d, *J* = 16.1 Hz, 1H), 6.21 (dd, *J* = 16.2, 7.5 Hz, 1H), 5.80 (m, 1H), 5.05 (m, 2H), 2.43 (quint, *J* = 6.7 Hz, 1H), 2.17 (m, 2H), 1.13 (t, *J* = 6.7 Hz, 3H). **^{13}C-RMN** (300 MHz, $CDCl_3$): δ 138.7, 138.2, 136.8, 131.2 (q, J_{C-F} = 31.6 Hz), 129.3, 129.0, 127.2, 126.1 (q, J_{C-F} = 272.4 Hz), 123.5 (q, J_{C-F} = 3.6 Hz), 122.8 (q, J_{C-F} = 3.6 Hz), 116.3, 41.3, 37.0, 19.9. **HRMS-EI$^+$** m/z calculated for $C_{14}H_{15}F_3$ **[M]$^+$:** 240.1126, found 240.1119.

Compound **IV-3j** was obtained in 97:3 enantiomeric ratio determined by chiral GC-MS using CP-Chirasil Dex CB (60→110 °C @ 10 °C/min, hold 2 min, then →180 °C @ 0.5 °C/min, flow rate 1.0 mL/min.). τ_{major} = 82.8 min, τ_{minor} = 81.1 min. **[α]$^{20}_D$** = +21.7 (*c* = 1.0, $CHCl_3$).

(+)-(*S*,*E*)-(3-Ethylhexa-1,5-dien-1-yl)benzene, **IV-3k**.



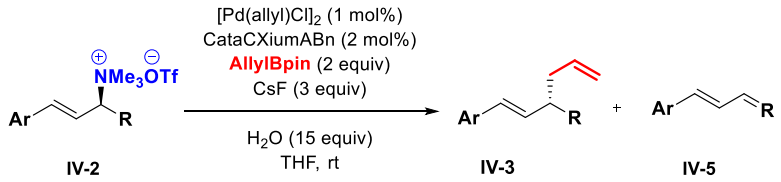
IV-3k

From (*S*,*E*)-methyl (1-phenylpent-1-en-3-yl) carbonate (44.1 mg, 0.2 mmol), following the general procedure described above but modifying the temperature to 35 ºC, compound **IV-3k** (26 mg, 0.14 mmol) was obtained in 70% yield as a colorless oil after flash column chromatography in hexane along with 28% of elimination product. The byproduct was removed by treating the mixture with maleic anhydride in THF at 60 ºC for 3 h.[22]

^{1}H-RMN (300 MHz, $CDCl_3$): δ 7.38-7.17 (m, 5H), 6.39 (d, *J* = 15.9 Hz, 1H), 6.03 (dd, *J* = 15.9, 7.9 Hz, 1H), 5.80 (m, 1H), 2.19 (m, 3H), 1.37 (m, 2H), 0.91 (t, *J* = 7.3 Hz, 3H), 0.87 (m, 2H). **^{13}C-RMN** (300 MHz, $CDCl_3$): δ 138.0, 137.1, 134.7, 129.9, 128.6, 126.9, 126.1, 115.9, 44.9, 39.5, 27.6, 11.8. **HRMS-GCEI$^+$** m/z calculated for $C_{14}H_{19}$ **[M]$^+$:** 187.1487, found 187.1465.

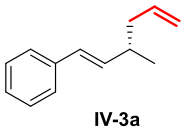
Compound **IV-3k** was obtained in 99:1 enantiomeric ratio determined by chiral GC-MS using CP-Chirasil Dex CB (60→120 °C @ 10 °C/min, then →145 °C @ 0.5 °C/min, then →180 °C @ 20 °C/min; flow rate 1.0 mL/min.). τ_{major} = 35.2 min, τ_{minor} = 35.0 min. $\mathbf{[\alpha]^{20}_D}$ = +13.6 (*c* = 1.0, $CHCl_3$).

4.5.3. Palladium-catalyzed allyl-allyl cross-coupling reaction of allylic ammonium salts.



In a 1 dram vial provided with a PTFE septa cap were weighted $[Pd(allyl)Cl]_2$ (0.7 mg, 0.002 mmol, 1 mol%) and the ligand di(1-adamantyl)benzylphosphine (CataCXiumABn) (1.6 mg, 0.004 mmol, 2 mol%). The vial was introduced to a glove box under nitrogen atmosphere and THF (0.2 mL) was added. The mixture was stirred 10 minutes at rt. To this solution, the ammonium salt **IV-2** (0.2 mmol) in THF (1.2 mL) was added and then, the allyl pinacol boronic ester (2 equiv), CsF (3 equiv), were added subsequently. Finally, the vial was taken out of the glove box and H_2O (15 equiv) was added. The reaction mixture was stirred overnight at rt. The reaction was filtered through a short pad of celite and rinsed with DCM. The solvent was evaporated under reduced pressure and the crude product purified by flash column chromatography using hexane as eluent. The ratio of **IV-3** and **IV-5** was determined by ^{1}H-RMN. Yields are corrected based on the amount of elimination product isolated with the desired product.

(+)-(*S*,*E*)-(3-Methylhexa-1,5-dien-1-yl)benzene, **IV-3a**.



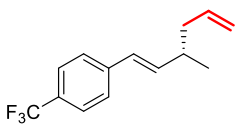
From (*S*,*E*)-*N*,*N*,*N*-trimethyl-4-phenylbut-3-en-2-aminium trifluoromethanesulfonate (67.8 mg, 0.2 mmol), following the general procedure described above, compound **IV-3a** (28 mg, 0.16 mmol) was obtained in 82% yield as

a colorless oil after flash column chromatography in hexane along with 6% of elimination product.

^{1}H-RMN (300 MHz, $CDCl_3$): δ 7.42-7.22 (m, 5H), 6.39 (d, *J* = 15.5 Hz, 1H), 6.22 (dd, *J* = 16.1, 7.4 Hz, 1H), 5.86 (m, 1H), 5.08 (m, 2H), 2.46 (quint, *J* = 6.6 Hz, 1H), 2.22 (m, 2H), 1.16 (t, *J* = 6.8 Hz, 3H). **^{13}C-RMN** (300 MHz, $CDCl_3$): δ 137.9, 137.1, 136.2, 128.6, 128.3, 127.0, 126.1, 116.1, 41.4, 37.0, 20.0.

Compound **IV-3a** was obtained in 96:4 enantiomeric ratio determined by chiral GC-MS using CP-Chirasil Dex CB (60→110 °C @ 10 °C/min, hold 2 min, then →130 °C @ 1 °C/min, then →180 °C @ 10 °C/min; flow rate 1.0 mL/min.). τ_{major} = 21.8 min, τ_{minor} = 22.2 min. **$[\alpha]^{20}_{D}$** = +38.7 (*c* = 1.0, $CHCl_3$).

(+)-(*S*,*E*)-1-(3-Methylhexa-1,5-dien-1-yl)-4-(trifluoromethyl)benzene, **IV-3d**.



IV-3d

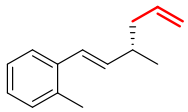
From (*S*,*E*)-*N*,*N*,*N*-trimethyl-4-(4-(trifluoromethyl)phenyl)but-3-en-2-aminium trifluoromethanesulfonate (81.4 mg, 0.2 mmol), following the general procedure described above, compound **IV-3d** (34 mg, 0.14 mmol) was obtained in 70% yield as a colorless oil after flash column chromatography in hexane along with 14% of elimination product.

^{1}H-RMN (300 MHz, $CDCl_3$): δ 7.54 (d, *J* = 8.2 Hz, 2H), 7.43 (d, *J* = 8.2 Hz, 2H), 6.39 (d, *J* = 16.0 Hz, 1H), 6.25 (dd, *J* = 15.9, 7.2 Hz, 1H), 5.80 (m, 1H), 5.13 – 4.97 (m, 2H), 2.44 (hept, *J* = 6.9 Hz, 1H), 2.29 – 2.07 (m, 2H), 1.12 (d, *J* = 6.7 Hz, 3H). **^{13}C-RMN** (300 MHz, $CDCl_3$): 141.5, 139.0, 136.8, 128.8 (q, J_{C-F} = 32.5 Hz), 127.2, 126.3, 125.6 (q, J_{C-F} = 3.8 Hz), 124.4

(q, $J_{C\text{-}F}$ = 272 Hz), 116.4, 41.3, 37.1, 19.9. **HRMS-EI$^+$** m/z calculated for $C_{14}H_{15}F_3$ **[M]$^+$:** 240.1126, found 240.1117.

Compound **IV-3d** was obtained in 97:3 enantiomeric ratio determined by chiral GC-MS using CP-Chirasil Dex CB (60→110 °C @ 10 °C/min, hold 2 min, then →130 °C @ 1 °C/min, then →180 °C @ 10 °C/min; flow rate 1.0 mL/min.). τ_{major} = 25.5 min, τ_{minor} = 25.4 min. **[α]$^{20}_D$** = +11.5 (*c* = 1.0, $CHCl_3$).

(+)-(*S*,*E*)-1-Methyl-2-(3-methylhexa-1,5-dien-1-yl)benzene, **IV-3f**.



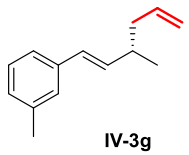
IV-3f

From ammonium salt (*S*,*E*)-*N*,*N*,*N*-trimethyl-4-(*o*-tolyl)but-3-en-2-aminium trifluoromethanesulfonate (70.7 mg, 0.2 mmol), following the general procedure described above, compound **IV-3f** (31 mg, 0.16 mmol) was obtained in 82% yield as a colorless oil after flash column chromatography in hexane along with 4% of elimination product.

^{1}H-RMN (300 MHz, $CDCl_3$): δ 7.39 (d, *J* = 6.3 Hz, 1H), 7.13 (m, 3H), 6.52 (d, *J* = 15.5 Hz, 1H), 5.99 (dd, *J* = 15.6, 7.4 Hz, 1H), 5.82 (m, 1H), 5.04 (m, 2H), 2.43 (quint, *J* = 6.7 Hz, 1H), 2.33 (s, 3H), 2.19 (m, 2H), 1.10 (t, *J* = 6.8 Hz, 3H). **^{13}C-RMN** (300 MHz, $CDCl_3$): δ 137.6, 137.1, 135.1, 130.2, 126.9, 126.2, 126.1, 125.6, 116.0, 41.6, 37.3, 20.2, 19.9. **HRMS-EI$^+$** m/z calculated for $C_{14}H_{18}$ **[M]$^+$:** 186.1409, found 186.1412.

Compound **IV-3f** was obtained in 96:4 enantiomeric ratio determined by chiral GC-MS using CP-Chirasil Dex CB., τ_{major} = 25.5 min, τ_{minor} = 25.1 min. **[α]$^{20}_D$** = +28.4 (*c* = 1.0, $CHCl_3$).

(+)-(*S*,*E*)-1-Methyl-3-(3-methylhexa-1,5-dien-1-yl)benzene, **IV-3g**.

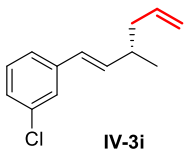

IV-3g

From ammonium salt (*S*,*E*)-*N*,*N*,*N*-trimethyl-4-(*m*-tolyl)but-3-en-2-aminium trifluoromethanesulfonate (70.6 mg, 0.2 mmol), following the general procedure described above, compound **IV-3g** (31 mg, 0.17 mmol) was obtained in 84% yield as a colorless oil after flash column chromatography in hexane along with 9% of elimination product.

^{1}H-RMN (300 MHz, $CDCl_3$): δ 7.15-7.05 (m, 3H), 6.94 (s broad, 1H), 6.28 (d, *J* = 15.5 Hz, 1H), 6.04 (dd, *J* = 15.9, 7.4 Hz, 1H), 5.72 (m, 1H), 4.95 (m, 2H), 2.31 (quint, *J* = 6.7 Hz, 1H), 2.25 (s, 3H), 2.06 (m, 2H), 1.02 (t, *J* = 6.7 Hz, 3H). **^{13}C-RMN** (300 MHz, $CDCl_3$): δ 138.1, 137.9, 137.1, 136.0, 128.5, 128.4, 127.8, 126.8, 123.3, 116.0, 41.5, 37.0, 21.5, 20.1. **HRMS-EI$^+$** m/z calculated for $C_{14}H_{18}$ **[M]$^+$:** 186.1409, found 186.1407.

Compound **IV-3g** was obtained in 97:3 enantiomeric ratio determined by chiral GC-MS using CP-Chirasil Dex CB(60→110 °C @ 10 °C/min, hold 2 min, then →130 °C @ 1 °C/min, then →180 °C @ 10 °C/min; flow rate 1.0 mL/min.). τ_{major} = 25.5 min, τ_{minor} = 25.3 min. **$[\alpha]^{20}_{D}$** = +27.6.

(+)-(*S*,*E*)-1-Chloro-3-(3-methylhexa-1,5-dien-1-yl)benzene, **IV-3i**.



IV-3i

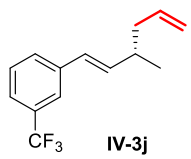
From (*S*,*E*)-4-(3-chlorophenyl)-*N*,*N*,*N*-trimethylbut-3-en-2-aminium trifluoromethanesulfonate (74.7 mg, 0.2 mmol), following the general procedure described above, compound **IV-3i** (38 mg, 0.18 mmol) was obtained in 92% yield as a colorless oil after flash column chromatography in hexane along with 7% of elimination product.

^{1}H-RMN (300 MHz, $CDCl_3$): δ 7.25 (s broad, 1H), 7.14-7.06 (m, 3H), 6.19 (d, *J* = 15.9 Hz, 1H), 6.06 (dd, *J* = 15.9, 7.2 Hz, 1H), 5.71 (m, 1H),

4.96 (m, 2H), 2.32 (quint, *J* = 6.6 Hz, 1H), 2.07 (m, 2H), 1.01 (t, *J* = 6.7 Hz, 3H). **^{13}C-RMN** (300 MHz, $CDCl_3$): δ 139.8, 137.7, 136.8, 134.5, 129.8, 127.1, 126.9, 126.0, 124.3, 116.3, 41.3, 37.0, 19.9. **HRMS-EI$^+$** m/z calculated for $C_{13}H_{15}Cl$ **[M]$^+$:** 206.0862, found 206.0867.

Compound **IV-3i** was obtained in 99:1 enantiomeric ratio determined by chiral GC-MS using CP-Chirasil Dex CB (60→110 °C @ 10 °C/min, hold 2 min, then →130 °C @ 1 °C/min, then →180 °C @ 10 °C/min; flow rate 1.0 mL/min.). τ_{major} = 33.1 min, τ_{minor} = 33.3 min. **[α]$^{20}_D$** = +24.1 (*c* = 1.0, $CHCl_3$).

(+)-(*S*,*E*)-1-(3-Methylhexa-1,5-dien-1-yl)-3-(trifluoromethyl)benzene, **IV-3j**.



IV-3j

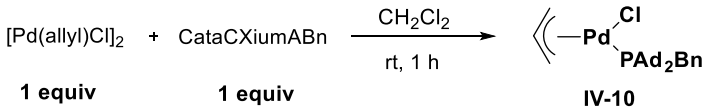
From (*S*,*E*)-4-(3-(Trifluoromethyl)phenyl)-*N*,*N*,*N*-trimethylbut-3-en-2-aminium trifluoromethanesulfonate (81.4 mg, 0.2 mmol), following the general procedure described above, compound **IV-3j** (22 mg, 0.09 mmol) was obtained in 46% yield as a colorless oil after flash column chromatography in hexane.

^{1}H-RMN (300 MHz, $CDCl_3$): δ 7.59 (s broad, 1H), 7.52-7.37 (m, 3H), 6.37 (d, *J* = 16.1 Hz, 1H), 6.21 (dd, *J* = 16.2, 7.5 Hz, 1H), 5.80 (m, 1H), 5.05 (m, 2H), 2.43 (quint, *J* = 6.7 Hz, 1H), 2.17 (m, 2H), 1.13 (t, *J* = 6.7 Hz, 3H). **^{13}C-RMN** (300 MHz, $CDCl_3$): δ 138.7, 138.2, 136.8, 131.2 (q, J_{C-F} = 31.6 Hz), 129.3, 129.0, 127.2, 126.1 (q, J_{C-F} = 272.4 Hz), 123.5 (q, J_{C-F} = 3.6 Hz), 122.8 (q, J_{C-F} = 3.6 Hz), 116.3, 41.3, 37.0, 19.9. **HRMS-EI$^+$** m/z calculated for $C_{14}H_{15}F_3$ **[M]$^+$:** 240.1126, found 240.1119.

Compound **IV-3j** was obtained in 96:4 enantiomeric ratio determined by chiral GC-MS using CP-Chirasil Dex CB (60→110 °C @ 10 °C/min, hold 2 min, then →130 °C @ 1 °C/min, then →180 °C @ 10 °C/min; flow

rate 1.0 mL/min.), τ_{major} = 22.1 min, τ_{minor} = 21.7 min. $[\alpha]^{20}_{D}$ = +21.7 (*c* = 1.0, $CHCl_3$).

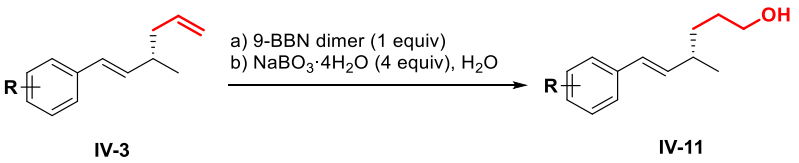
4.5.4. Synthesis of precatalyst **IV-10**.



Inside the glovebox, $[Pd(allyl)Cl]_2$ (25 mg, 0.068 mmol) and cataCXium ABn (53.6 mg, 0.068 mmol) were added to an oven dried 1-dram vial with a stir bar. Dichloromethane (2 mL) was added to the mixture and it was left stirring at room temperature for 18 h. After 18 h, the solid was filtered and re-crystallized from dichloromethane, obtaining product IV-10 (18 mg, 0.031 mmol) in 46% yield as a yellowish crystalline solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72 (d, J = 7.4 Hz, 2H), 7.17 (dt, J = 14.4, 7.2 Hz, 3H), 5.51 – 5.31 (m, 1H), 4.81 (td, J = 7.1, 2.4 Hz, 1H), 3.94 (d, J = 6.6 Hz, 1H), 3.82 – 3.68 (m, 1H), 3.68 – 3.45 (m, 2H), 2.72 (d, J = 11.9 Hz, 1H), 2.31 – 2.17 (m, 2H), 2.17 – 1.96 (m, 6H), 1.97 – 1.82 (m, 10H), 1.72 – 1.52 (m, 12H). **^{13}C NMR** (76 MHz, $CDCl_3$) δ 136.7, 136.6, 131.0, 130.9, 127.9, 126.2, 126.2, 115.0, 114.9, 82.2, 81.9, 52.4, 52.4, 41.0, 40.8, 40.6, 40.5, 40.2, 40.01, 39.98, 36.5, 28.7, 28.64, 28.61, 28.5, 24.6, 24.4.

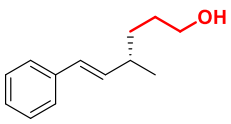
4.5.5. General procedure for the selective hydroboration of dienes **IV-3**.



IV-3 **IV-11**

To an oven-dried 1 dram vial with a stir bar was added 9-BBN dimer (1 equiv) and THF (5 mL/mmol) under N_2. The solution was cooled to 0 ºC and a solution of diene **IV-3** (1 equiv) in THF (5 mL/mmol) was added slowly. The solution was warmed to rt and left stirring for 16 h. After full conversion (checked by ^{1}H-NMR), water (10 mL/mmol) was added, followed by $NaBO_3 \cdot 4H_2O$ and the mixture was stirred for 3 h. The reaction mixture was extracted with Et_2O (3x) and the combined organic layers were washed with brine, dried over MgSO4 and the solvent evaporated. The crude reaction was purified by flash column chromatography using *n*-hexane/AcOEt (9:1) as eluent.

(+)-(*S*,*E*)-4-Methyl-6-phenylhex-5-en-1-ol, **IV-11a**.



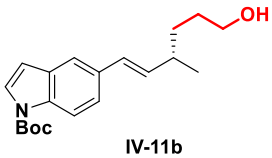
IV-11a

From (*S*,*E*)-(3-methylhexa-1,5-dien-1-yl)benzene (34.5 mg, 0.2 mmol), following the general procedure described above, compound **IV-11a** (31 mg, 0.16 mmol) was obtained in 82% yield as a colorless oil after flash column chromatography.

^{1}H-RMN (300 MHz, $CDCl_3$): δ 7.32 – 7.17 (m, 4H), 7.17 – 7.05 (m, 1H), 6.28 (d, *J* = 15.9 Hz, 1H), 6.01 (dd, *J* = 15.9, 8.0 Hz, 1H), 3.57 (t, *J* = 6.5 Hz, 2H), 2.24 (hept, *J* = 6.7 Hz, 1H), 1.53 (m, 2H), 1.38 (m, 2H), 1.03 (d, *J* = 6.7 Hz, 3H). **^{13}C-RMN** (300 MHz, $CDCl_3$): δ 137.8, 136.4, 128.5, 128.5, 126.9, 126.0, 63.1, 37.2, 33.1, 30.7, 20.7. **HRMS-GCEI$^+$** m/z

calculated for $C_{13}H_{18}O$ **[M]$^+$:** 190.1358, found 190.1356. **[α]$^{20}_D$** = +43.3 (*c* = 1.0, $CHCl_3$).

(+)-*tert*-Butyl-(*S*,*E*)-5-(6-hydroxy-3-methylhex-1-en-1-yl)-1H-indole-1-carboxylate, **IV-11b**.



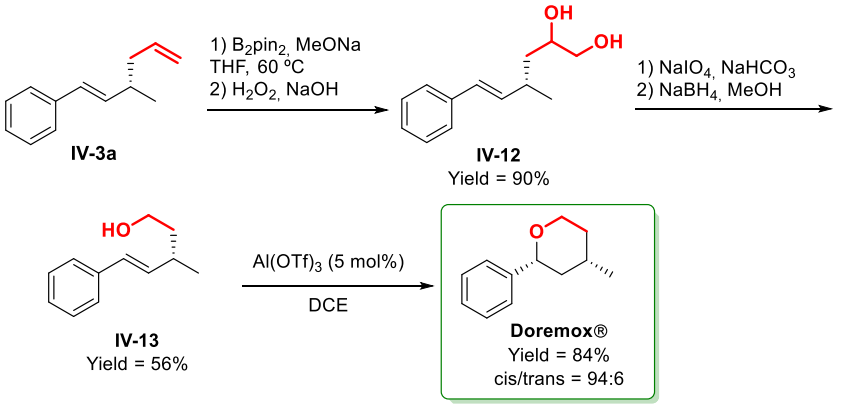
IV-11b

From (*S*,*E*)-*tert*-butyl-5-(3-methylhexa-1,5-dien-1-yl)-1H-indole-1-carboxylate (62.3 mg, 0.2 mmol), following the general procedure described above, compound **IV-11b** (49 mg, 0.15 mmol) was obtained in 74% yield as a yellow oil after flash column chromatography.

^{1}H-RMN (300 MHz, $CDCl_3$): δ 8.04 (d, *J* = 8.6 Hz, 1H), 7.55 (d, *J* = 3.8 Hz, 1H), 7.50 (d, *J* = 1.7 Hz, 1H), 7.33 (dd, *J* = 8.6, 1.8 Hz, 1H), 6.52 (dd, *J* = 3.7, 0.8 Hz, 1H), 6.44 (d, *J* = 15.7 Hz, 1H), 6.08 (dd, *J* = 15.8, 8.0 Hz, 1H), 3.66 (t, *J* = 6.5 Hz, 2H), 2.33 (hept, *J* = 6.9 Hz, 1H), 1.67 (s, 10H), 1.62 (m, 2H), 1.48 (m, 2H), 1.12 (d, *J* = 6.7 Hz, 3H). **^{13}C-RMN** (300 MHz, $CDCl_3$): δ 149.7, 135.2, 134.4, 132.6, 130.9, 128.7, 126.2, 122.5, 118.3, 115.1, 107.4, 83.6, 63.2, 37.2, 33.2, 30.7, 28.2, 20.8. **HRMS-ESI$^+$** m/z calculated for $C_{20}H_{27}NO_3Na$ **[M+Na]$^+$:** 352.1883, found 352.1889.

Compound **IV-11b** was obtained in 95:5 enantiomeric ratio determined by chiral HPLC using Chiralpak-IA column [Hexane/iPrOH (98:2)], 1.0 mL/min, τ_{major} = 19.3 min, τ_{minor} = 18.0 min. **[α]$^{20}_D$** = +13.1 (*c* = 1.0, $CHCl_3$).

4.5.6. Synthesis of **Doremox®**.



To an oven-dried 1-dram vial with a stir bar was added MeONa (25.6 mg, 0.48 mmol, 0.6 equiv) and B_2pin_2 (464 mg, 1.6 mmol, 2 equiv) and solved in THF (2 mL) under N_2. The solution was cooled to 0 ºC and a solution of **IV-3a** (138 mg, 0.8 mmol, 1 equiv) in THF (2 mL) was added slowly. The solution was warmed to 60 ºC and left stirring for 16 h at that temperature. After full conversion (^{1}H-NMR), water was added, and the reaction mixture was extracted with Et_2O (3x) and the combined organic layers were washed with brine, dried over $MgSO_4$ and the solvent evaporated. The crude product was used without further purification in the next step.

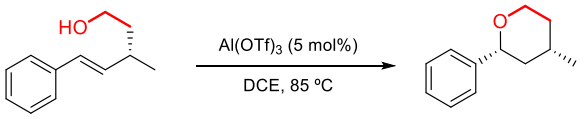
To an oven-dried flask with a stir bar, diborylated product was added (1 equiv) and solved in THF (3.2 mL). At this point, the mixture was cooled to 0 ºC and NaOH 1M (1.6 ml, 2 equiv) and H_2O_2 30% (0.32 mL). The solution was warmed to room temperature and left stirring for 2 h at that temperature. After full conversion (TLC), water was added, and the reaction mixture was extracted with Et_2O (3x) and the combined organic layers were washed with brine, dried over $MgSO_4$ and the solvent evaporated. The crude product was used without further purification in the next step.

To an oven-dried flask with a stir bar, the diol was added (1 equiv) and solved in DCM (1.2 mL). At this point the mixture was cooled to 0 ºC and $NaIO_4$ (344 mg, 0.8 mmol, 2 equiv) and saturated $NHCO_3$ solution (80 µL) were added. The solution was warmed to room temperature and left stirring for 16 h at that temperature. After full conversion (TLC), water was added, and the reaction mixture was extracted with DCM (3x) and the combined organic layers were washed with brine, dried over $MgSO_4$ and the solvent evaporated. The crude product was used without further purification in the next step.

To an oven-dried round bottom flask was added the aldehyde (1 equiv) in methanol (0.3M) and cooled to 0 ºC. To this solution, sodium borohydride (44 mg, 1.16 mmol, 1.45 equiv) was added portionwise and the reaction mixture was stirred for 1 h at 0 ºC. Then, the mixture was warmed until room temperature and stirred until full conversion. The reaction mixture was quenched with ammonium chloride saturated aqueous solution and extracted with diethyl ether for three times, dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography on silica gel using *n*-hexane/AcOEt (9:1) as eluent. Alcohol **IV-13** (90 mg, 0.52 mmol) was obtained in 50% yield after 4 steps as a colorless oil.

^{1}H NMR, **^{13}C NMR** and **MS** data were consistent with literature values.[43] **^{1}H-RMN** (300 MHz, $CDCl_3$): δ 7.32-7.15 (m, 5H), 6.32 (d, *J* = 15.9 Hz, 1H), 6.02 (dd, *J* = 15.8, 7.2 Hz, 1H), 3.63 (t, *J* = 6.5 Hz, 2H), 2.42 (hept, *J* = 7.2 Hz, 1H), 1.66-1.45 (m, 2H), 1.05 (d, *J* = 7.2 Hz, 3H).

[43] Coulombel, L.; Weïwer, M.; Duñach, E. *Eur. J. Org. Chem.*, **2009**, *33*, 5788.



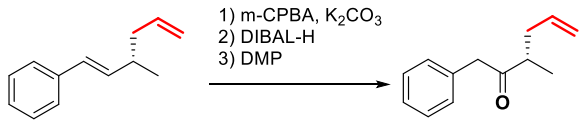
IV-13

Doremox®
Yield = 82%
d.r. = 94:6

Over a solution of **IV-13** (52.9 mg, 0.3 mmol) in DCE (3 mL), $Al(OTf)_3$ (7.1 mg, 0.015 mmol, 0.05 equiv) was added and the reaction was stirred at 85 ºC for 3 h. After full conversion (GC-MS), the reaction was cooled to 0 ºC and HCl 1N was added. The reaction mixture was extracted with diethyl ether for three times, dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography on silica gel using *n*-pentane/Et_2O (9:1) as eluent. **Doremox®** (44 mg, 0.25 mmol) was obtained in 84% yield and d.r. = 94:6 as a colorless oil.

^{1}H-RMN (300 MHz, $CDCl_3$): δ 7.30-7.14 (m, 5H), 4.24 (dd, *J* = 11.3 Hz, 2.1 Hz, 1H), 4.14-4.03 (ddd, *J* = 11.3, 4.8, 1.5 Hz, 1H), 3.60-3.46 (ddd, *J* = 12.3, 12.2, 2.3 Hz, 1H), 1.83-1.54 (m, 3H), 1.37-1.06 (m, 2H), 0.93 (d, *J* = 6.8 Hz, 3H). **^{13}C-RMN** (75 MHz, $CDCl_3$): δ 143.2, 128.3, 127.3, 126.1, 125.8, 79.8, 68.5, 42.7, 34.4, 30.81, 22.3. **HRMS-EI$^+$** m/z calculated for $C_{12}H_{16}O$ $[M]^+$: 176.1193, found 176.1201. **$[\alpha]^{20}_D$**= +44.8 (*c* = 1.0, $CHCl_3$). The absolute configuration was stablished by comparison with the previously reported compound.[25]

4.5.7. Synthesis of (+)-(*S*)-3-methyl-1-phenylhex-5-en-2-one, **IV-14**.



IV-3a **IV-13**
Yield = 82%

To an oven-dried round flask was added a solution of **IV-3a** (35 mg, 0.2 mmol) in DCM (3 mL). The mixture was cooled to 0 ºC and a solution of *m*-CPBA (44.6 mg, 0.2 mmol) in DCM (3 mL) was added slowly. Then, potassium carbonate (27.8 mg, 0.2 mg) was added and the mixture was slowly warmed to rt. The reaction was stirred for 16 h and then a solution of Na_2SO_3 was added to the mixture. The phases were separated, and the aqueous phase was extracted with Et_2O (3x). The combined organic phases were washed with $NaHCO_3$ (2x), brine, dried over $MgSO_4$ and the solvent evaporated. The crude mixture was filtered through a short pad of silica (*n*-hexane/EtOAc 99:1) and the desired epoxide was obtained as a 1:1 mixture of diastereoisomers, which was used in the next step of synthesis without further purification.

Over a solution of the epoxide (55 mg, 0.3 mmol) in DCM (2 mL) at -40 ºC, was added DIBAL-H (0.9 mL, 0.9 mmol). The reaction was stirred at rt until full conversion (TLC). Then, water was added slowly, and the phases were separated. The aqueous phase was extracted with Et_2O (3x) and the combined organic phases were washed with $NaHCO_3$ (2x), brine, dried over $MgSO_4$ and the solvent evaporated. The crude mixture was filtered through a short pad of silica (*n*-hexane/EtOAc 95:5) and the desired alcohol was obtained as a 1:1 mixture of diastereoisomers, which was used in the next step of synthesis without further purification.

To an oven-dried round flask was added a solution of the alcohol (39 mg, 0.2 mmol) in DCM (2 mL). The mixture was cooled to 0 ºC and DMP (110 mg, 0.3 mmol) was added slowly. The mixture was slowly warmed to rt and left stirred for 16 h. Then a solution of $Na_2S_2O_3$ was added to the mixture. The phases were separated, and the aqueous phase was extracted with Et_2O (3x). The combined organic phases were washed with $NaHCO_3$ (2x), brine, dried over $MgSO_4$ and the solvent evaporated. The crude reaction was purified by flash column chromatography using *n*-hexane/AcOEt (95:5) as eluent. Compound **IV-14** (37 mg, 0.19 mmol) was obtained in 82% yield (3 steps) as a colorless oil.

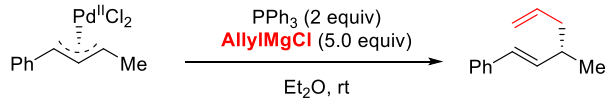
^{1}H-RMN (300 MHz, $CDCl_3$): δ 7.30-7.07 (m, 5H), 5.75-5.42 (m, 1H), 4.99-4.88 (m, 2H), 3.66 (s, 2H) 2.65 (hept, *J* = 6.9 Hz, 1H), 2.32 (m, 1H), 2.03 (m, 1H), 1.01 (d, *J* = 6.9 Hz, 3H). **^{13}C-RMN** (300 MHz, $CDCl_3$): δ 210.9, 135.5, 134.1, 129.5, 128.6, 126.9, 116.8, 77.4, 77.2, 76.6, 48.6, 45.1, 37.1, 16.2. **HRMS-EI$^+$** m/z calculated for $C_{13}H_{16}O$ $[M]^+$: 188.1204, found 188.1201. **$[\alpha]^{20}_D$**= +19.4 (*c* = 1.0, $CHCl_3$).

4.5.8. Assignment of the Absolute Configuration.

The absolute configuration was stablished for compounds, **IV-3a** and **Doremox®** by comparison of the sign of the optical rotation with that of previously reported compounds. Our results indicate that the palladium catalyzed cross-coupling reaction proceeds with inversion of the configuration. We assumed the same stereochemical outcome for all the enantiomerically enriched compounds prepared.

*4.5.8.1. (S,E)-(3-methylhexa-1,5-dien-1-yl)benzene, **IV-3a**.*[21]

Previously reported

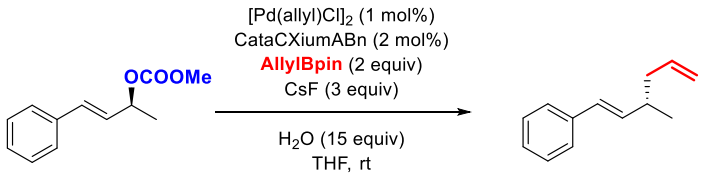


e.e. = 70%

60%
e.e. = 57%
$[\alpha]^{20}_D$ = +26.6 (c 2.0, C_6H_6).

J. Chem. Soc. Chem. Commun. **1984**, *18*, 107-108.

This work

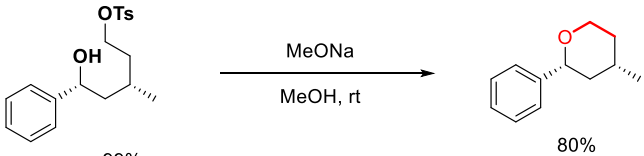


IV-1a

IV-3a
87%
e.r. = 98:2
$[\alpha]^{20}_D$ = +44.5 (c = 1.0, $CHCl_3$).

4.5.8.2. (2R,4S)-4-methyl-2-phenyltetrahydro-2H-pyran, ***Doremox®.***[25]

Previously reported

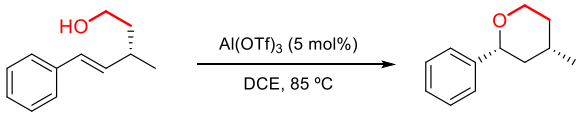


e.e. = 99%

80%
e.e. = 99%
$[\alpha]^{20}_{D}$ = +18.1 (c = 0.75, $CHCl_3$).

Can. J. Chem. **2002**, *80,* 714-723.

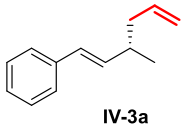
This work



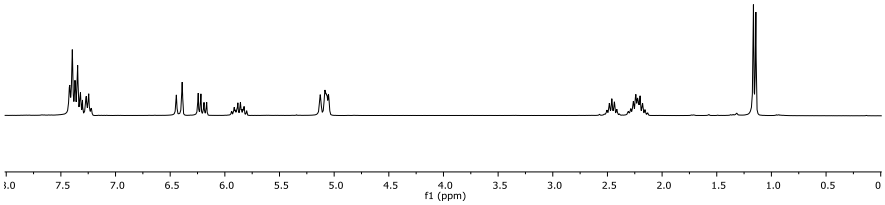
IV-13
e.r. = 98:2

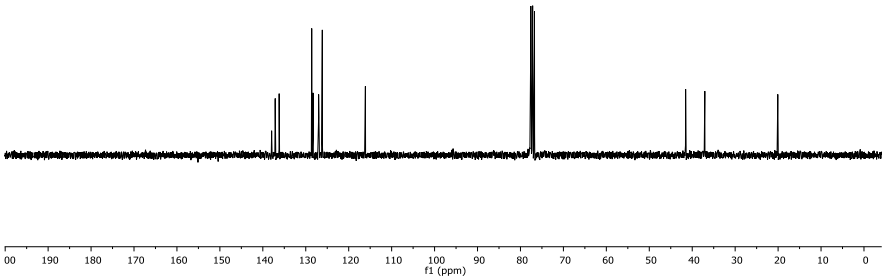
Doremox®
82%
d.r. = 94:6
$[\alpha]^{20}_{D}$ = +44.8 (c = 1.0, $CHCl_3$).

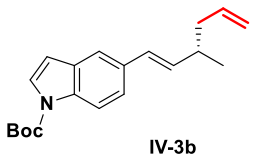
4.6. NMR spectra.



IV-3a



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IV-3b

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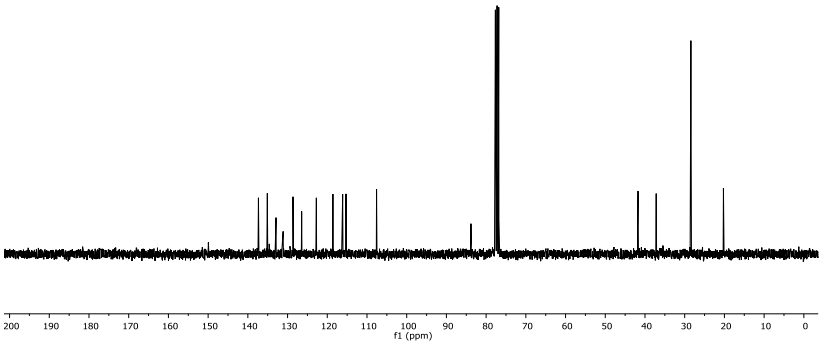
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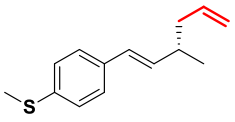
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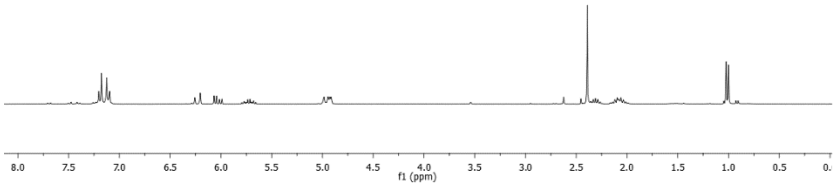
IV-3c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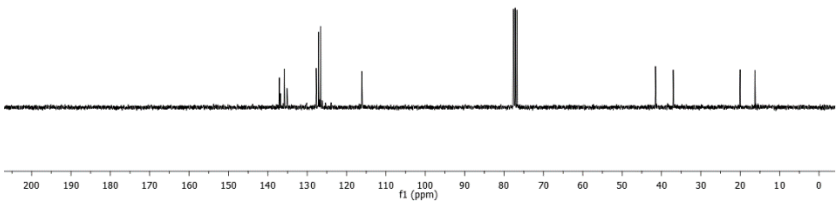
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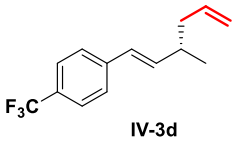
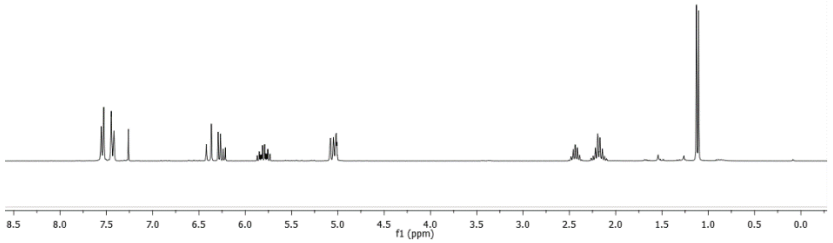

F3C

IV-3d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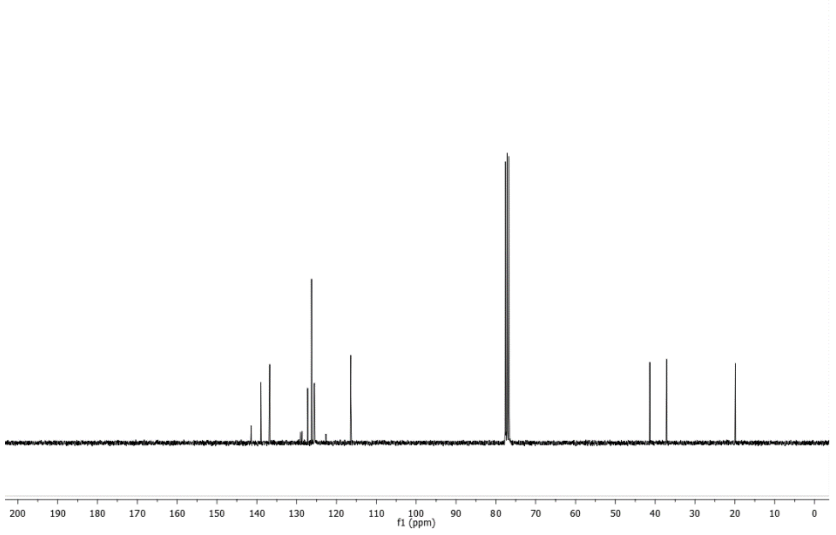
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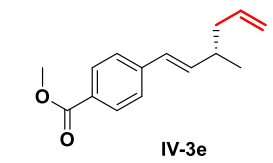
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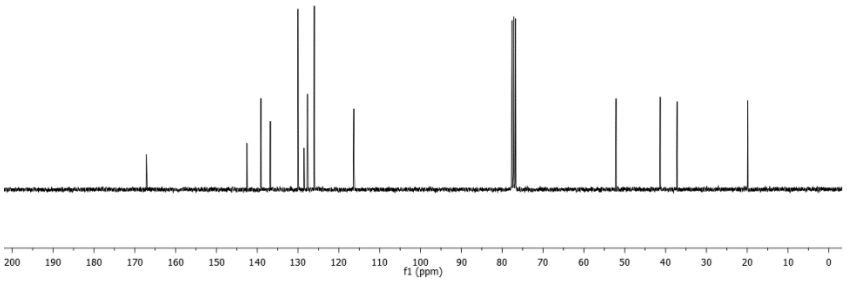
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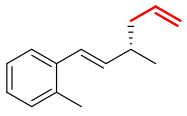
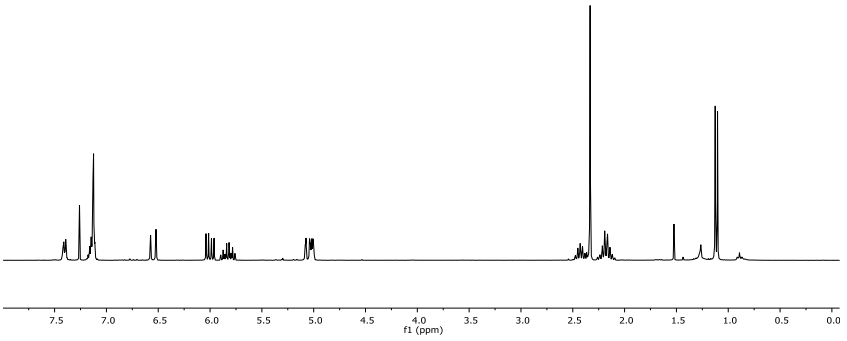


IV-3f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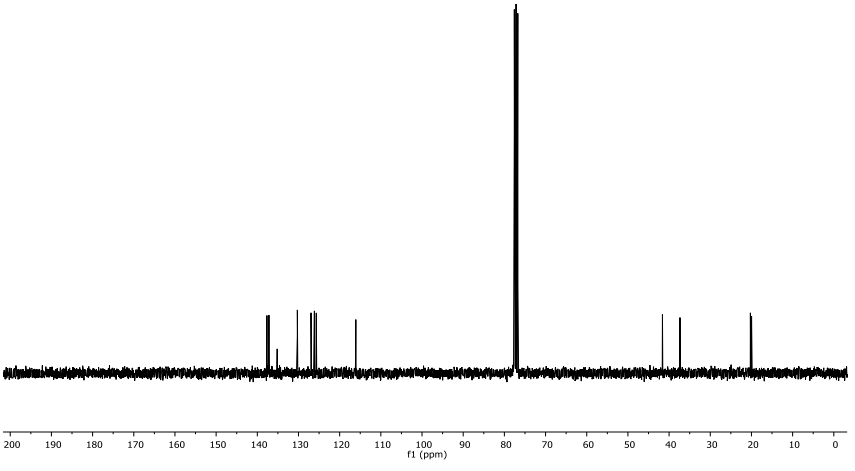
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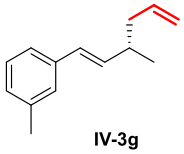

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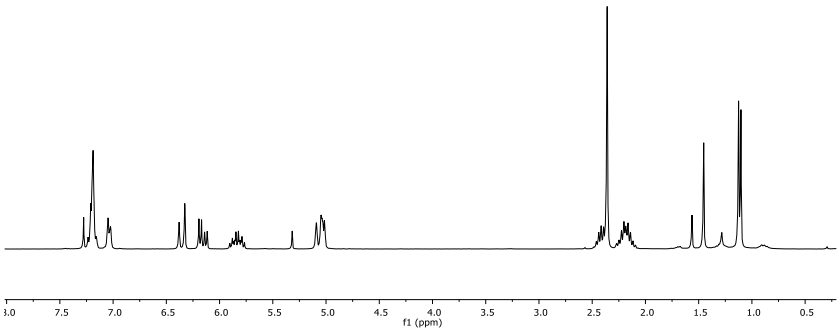
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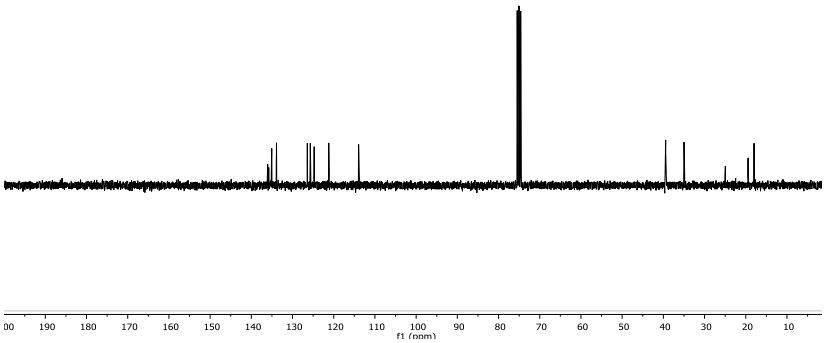
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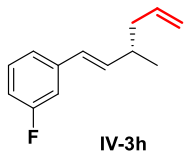
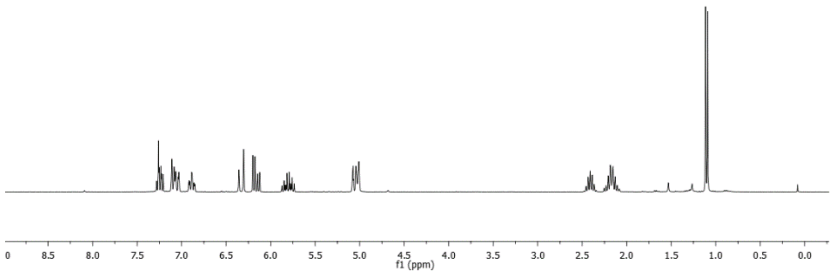

F

IV-3h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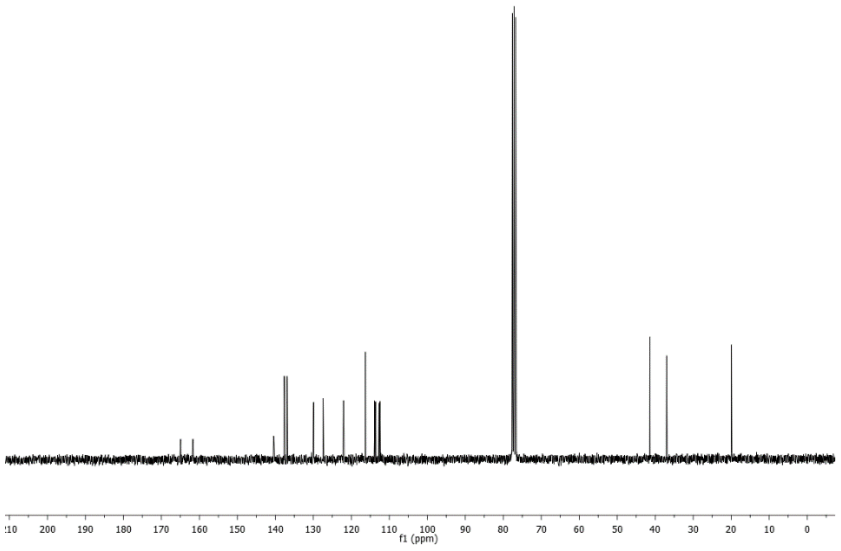
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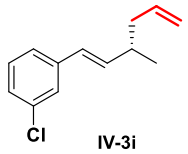
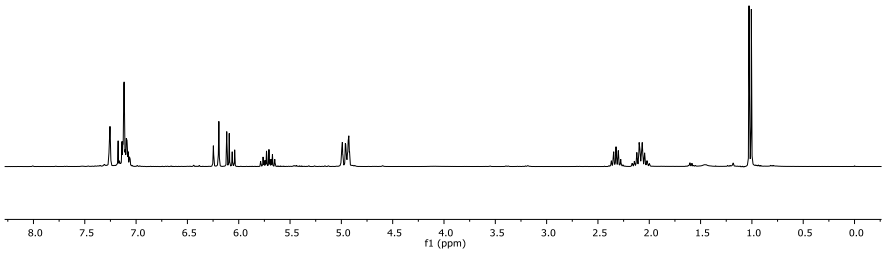
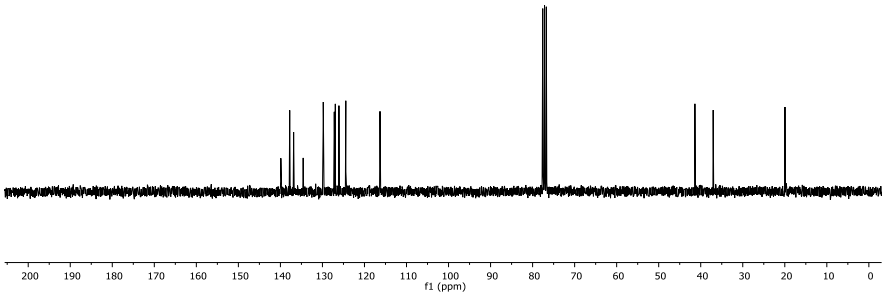
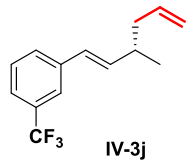
0
f1 (ppm)


Cl

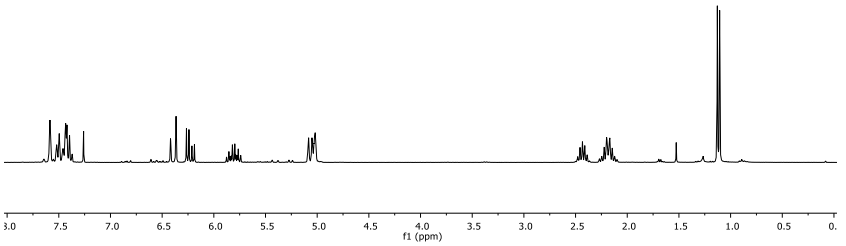
IV-3i

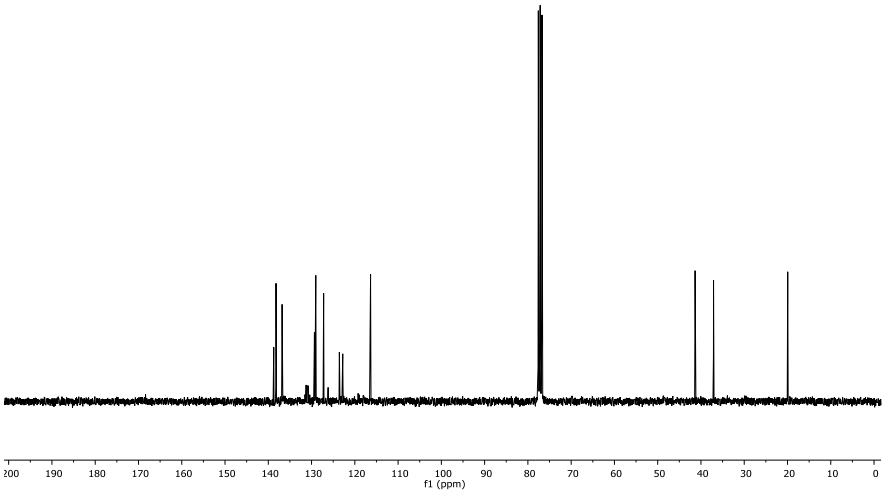

8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

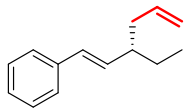

200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)



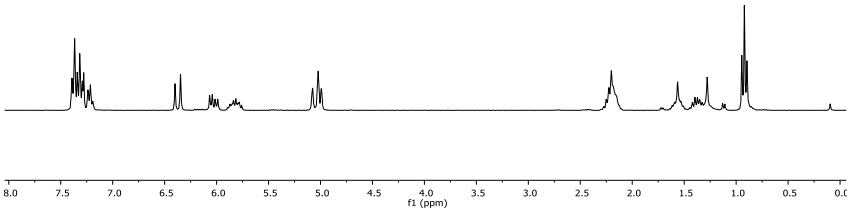
IV-3j

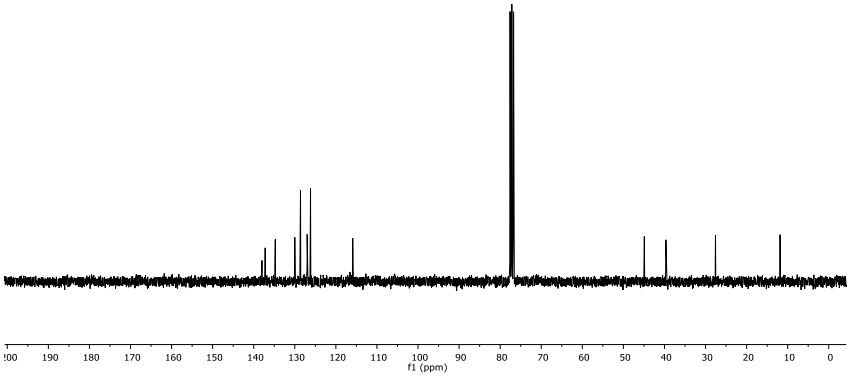


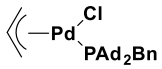




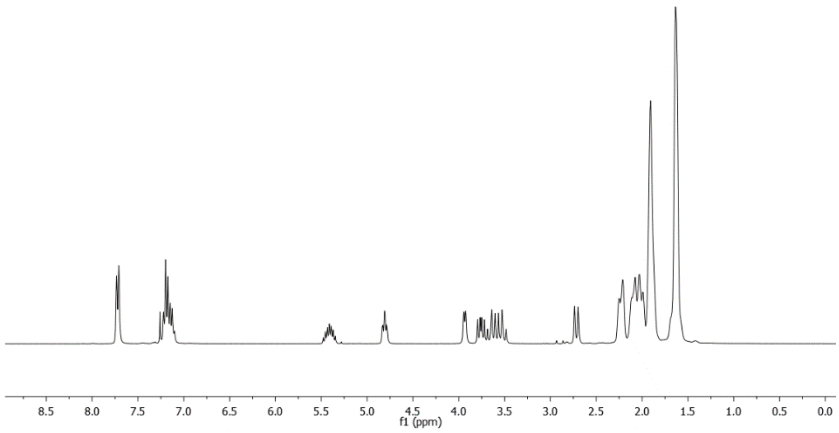
IV-3k

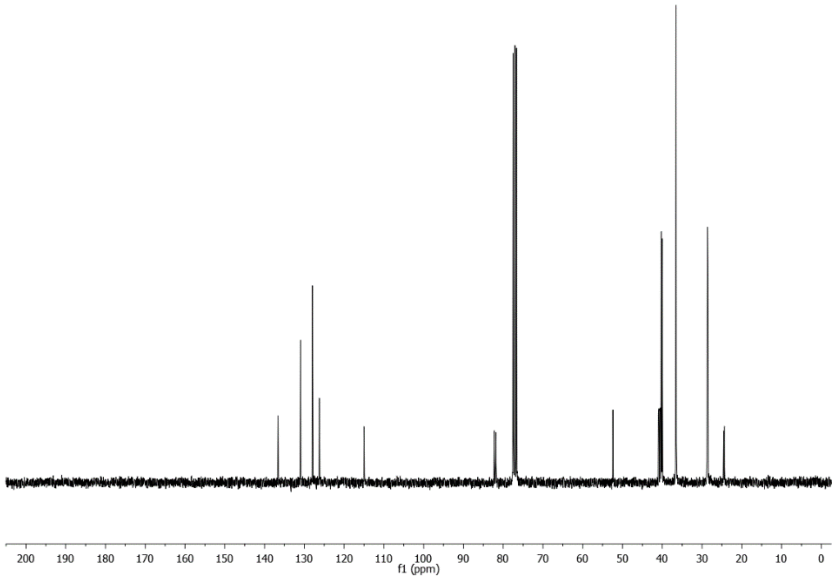

8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

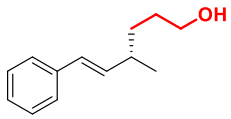

190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


Cl
Pd
PAd2Bn

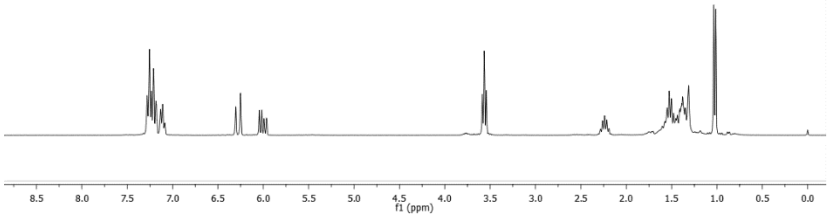
IV-10

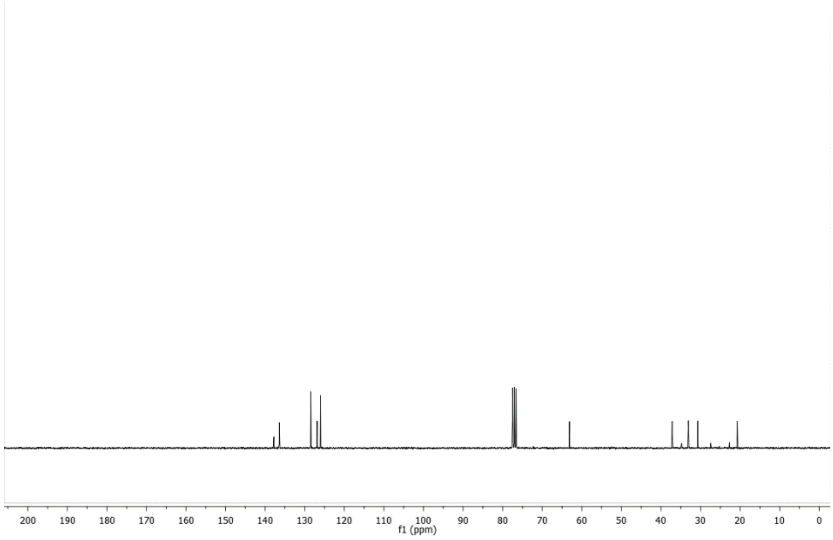

8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


OH

IV-11a


8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


200
190
180
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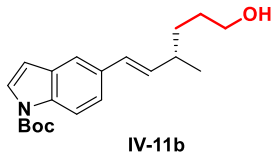
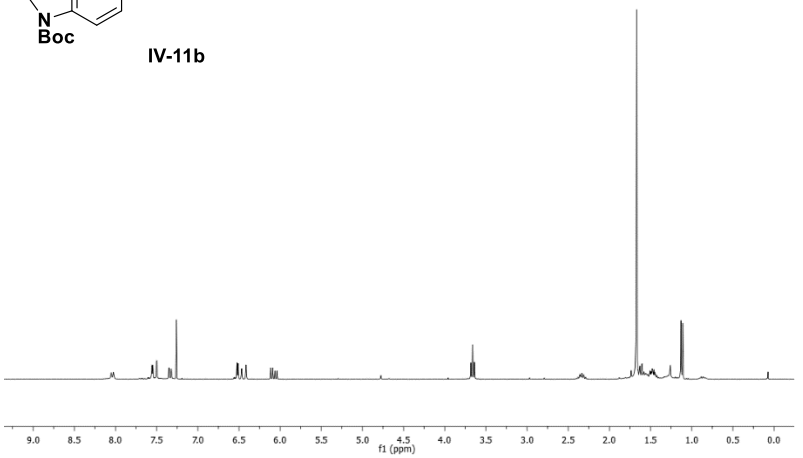
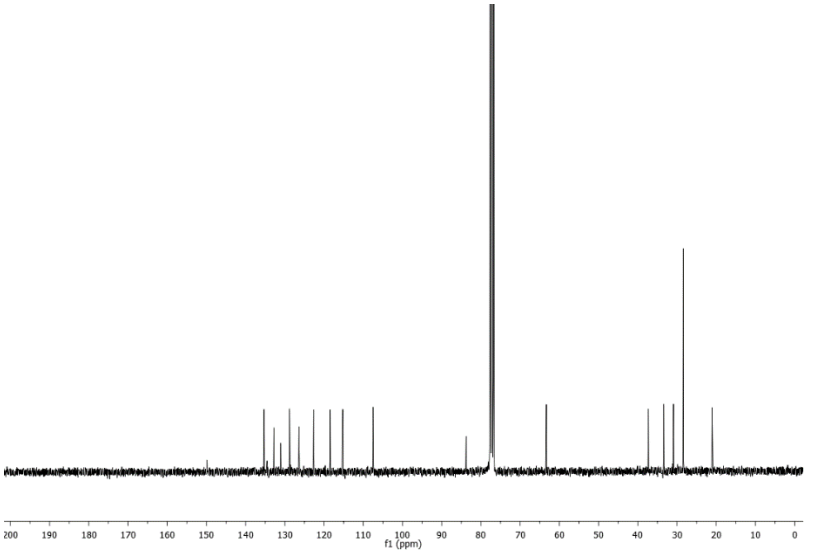
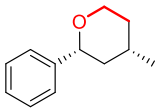
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


OH
N
Boc

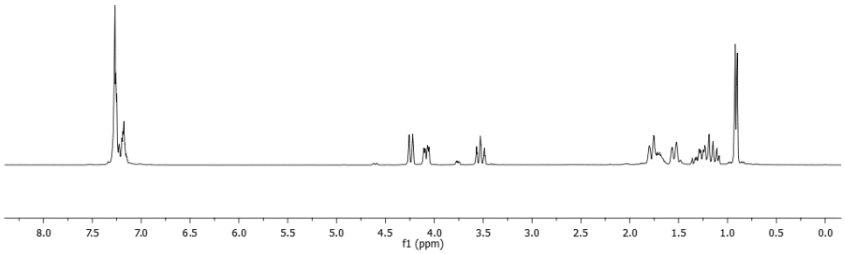
IV-11b

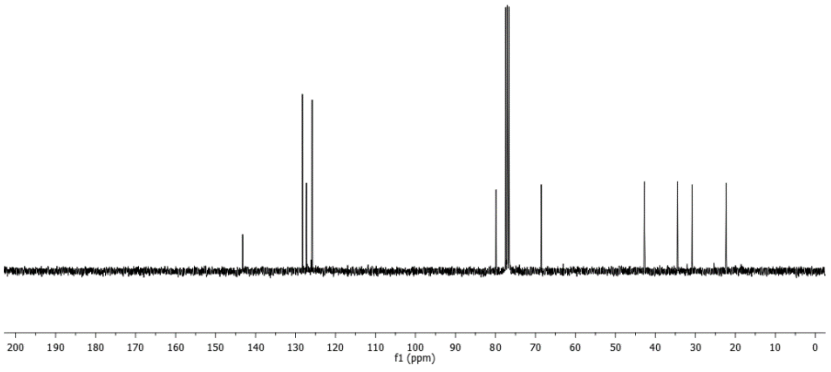

9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

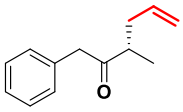

200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)



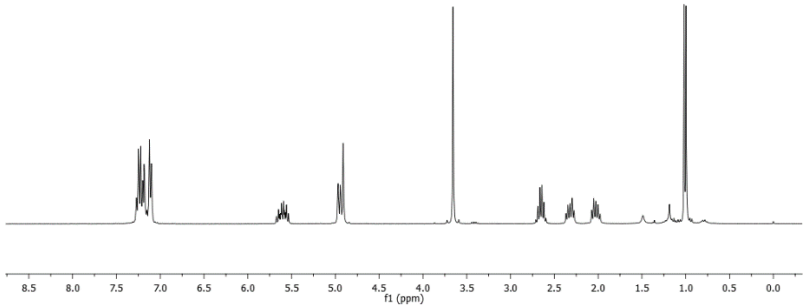
Doremox®

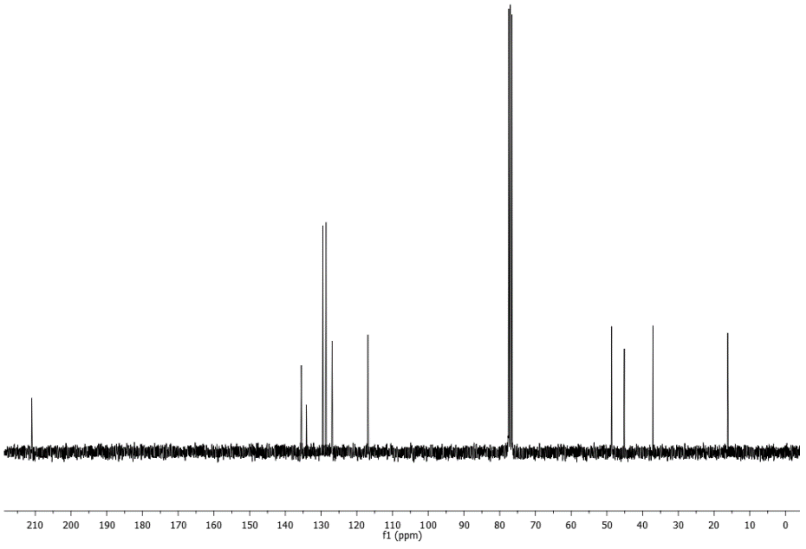

8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

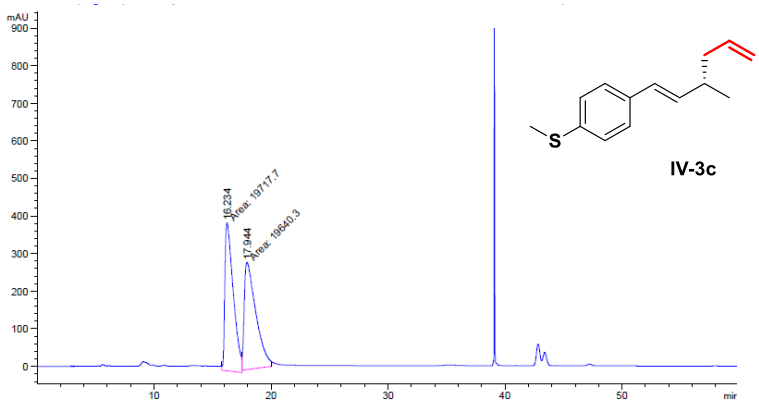

O

IV-14

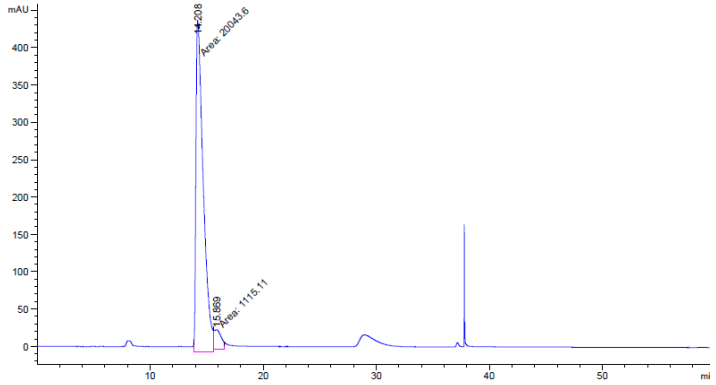

8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

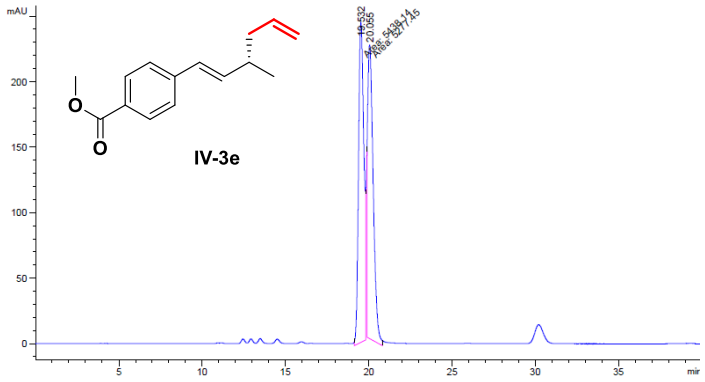
4.7. HPLC Chromatograms.



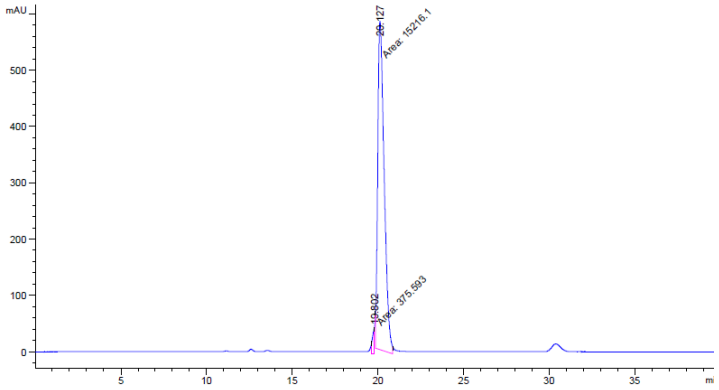
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.234	MM	0.8343	1.97177e4	393.89218	50.0984
2	17.944	MM	1.1475	1.96402e4	285.25943	49.9016
Totals :				3.93580e4	679.15161	



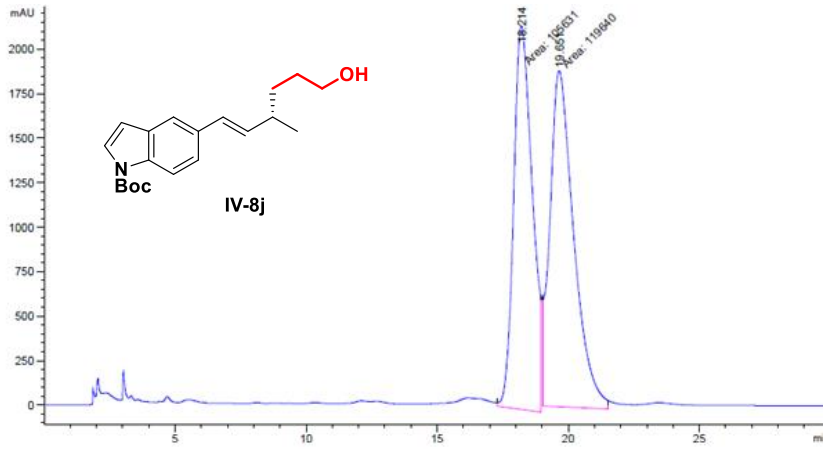
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.208	MM	0.7508	2.00436e4	444.96378	94.7298
2	15.869	MM	0.7060	1115.10791	26.32532	5.2702
Totals :				2.11587e4	471.28909	



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.532	MM	0.3705	5438.13672	244.60970	50.7498
2	20.055	MM	0.3920	5277.45215	224.39349	49.2502
Totals :				1.07156e4	469.00319	

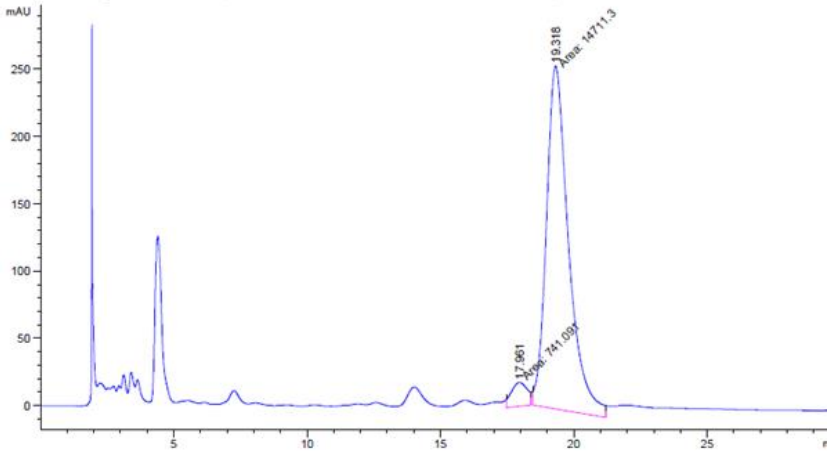


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.802	MM	0.1338	375.59253	46.78131	2.4089
2	20.127	MM	0.4354	1.52161e4	582.41290	97.5911
Totals :				1.55917e4	629.19421	



IV-8j

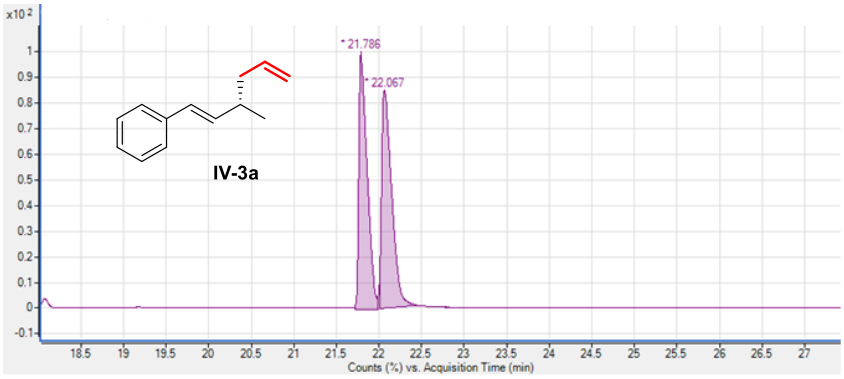
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.214	MM	0.8167	1.05631e5	2155.74683	46.8906
2	19.651	MM	1.0552	1.19640e5	1889.63440	53.1094



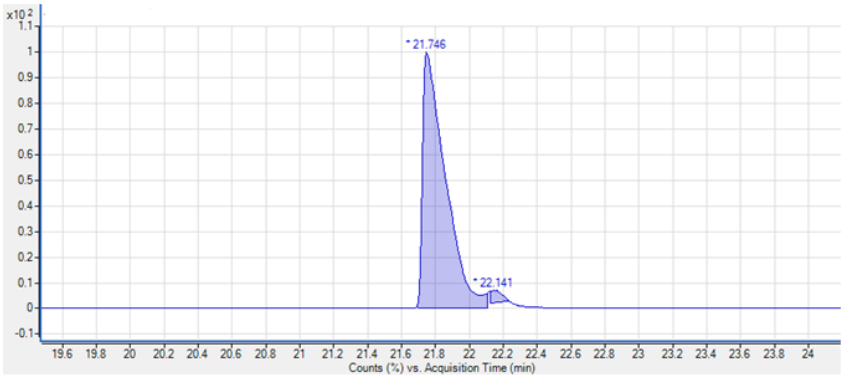
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.961	MM	0.6975	741.09058	17.70927	4.7960
2	19.318	MM	0.9616	1.47113e4	254.98064	95.2040
Totals :				1.54524e4	272.68991	

4.8. SFC Chromatograms.

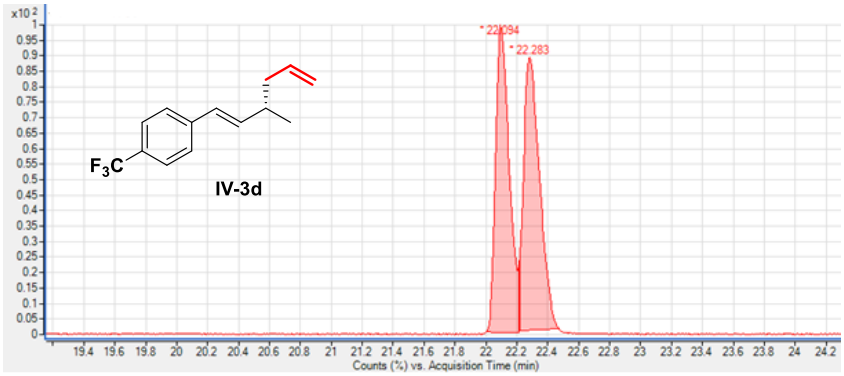
4.8.1. 1,5-dienes **IV-3** from **IV-1**.



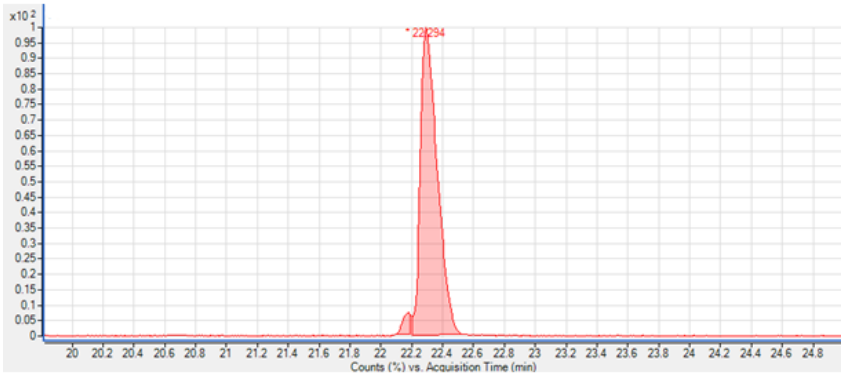
RT	Area	Area %
21.786	21275468.52	97.46
22.067	21830539.4	100



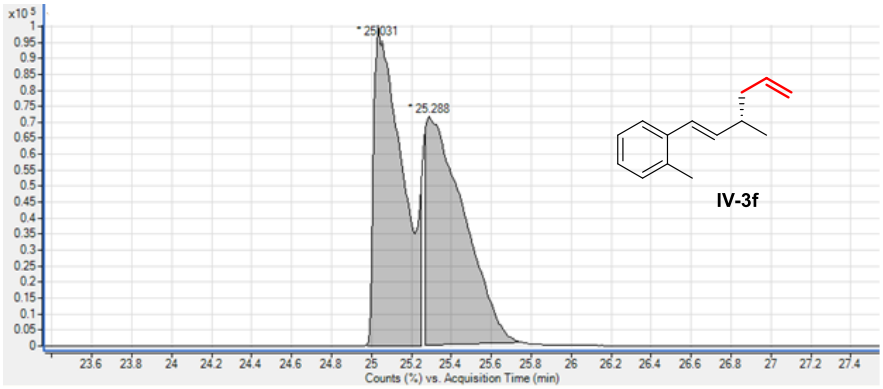
RT	Area	Area %
21.746	35170022.35	100
22.141	790280.45	2.25



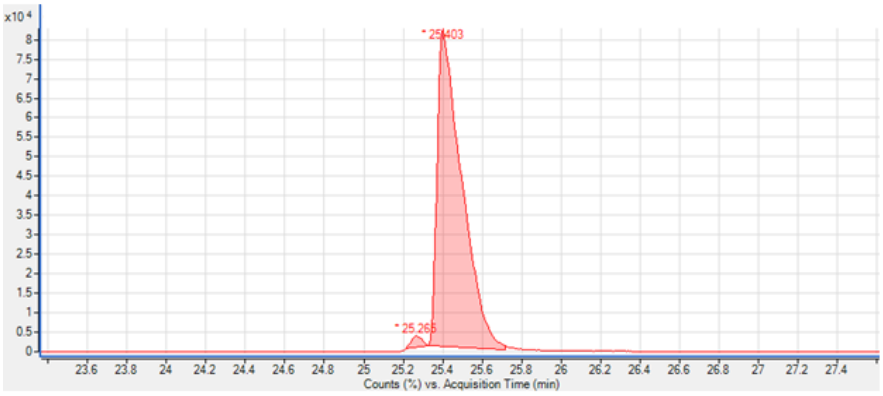
RT	Area	Area %
22.094	8397948.69	96.51
22.283	8701939.94	100



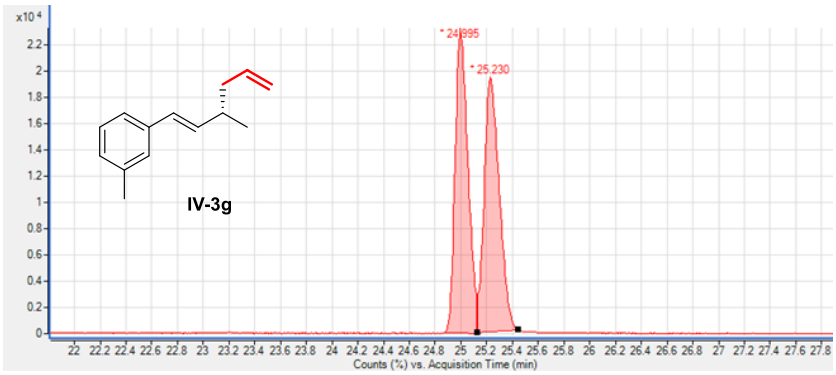
RT	Area	Area %
22.18	393116.64	3.05
22.294	12908004.5	100



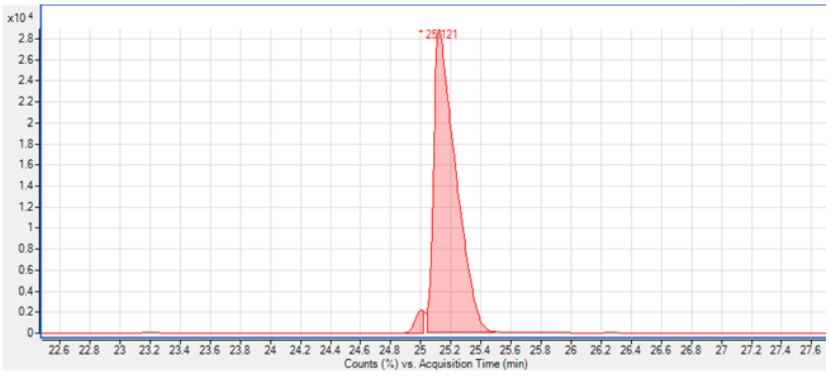
RT	Area	Area %
25.031	81714240.2	100
25.288	78788324.8	96.42



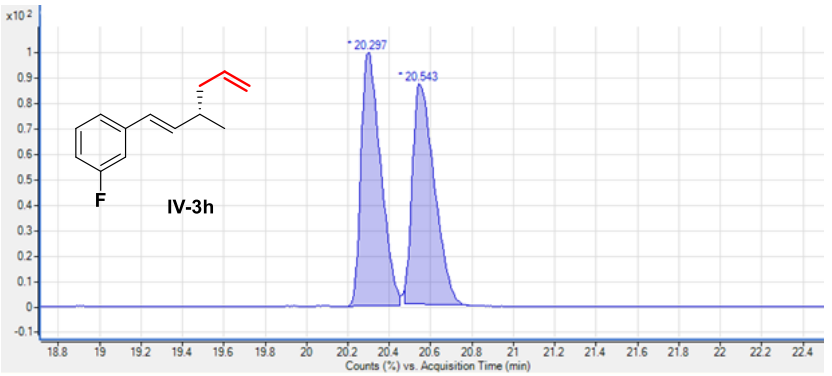
RT	Area	Area %
25.265	238482.96	1.5
25.403	15862788.	100



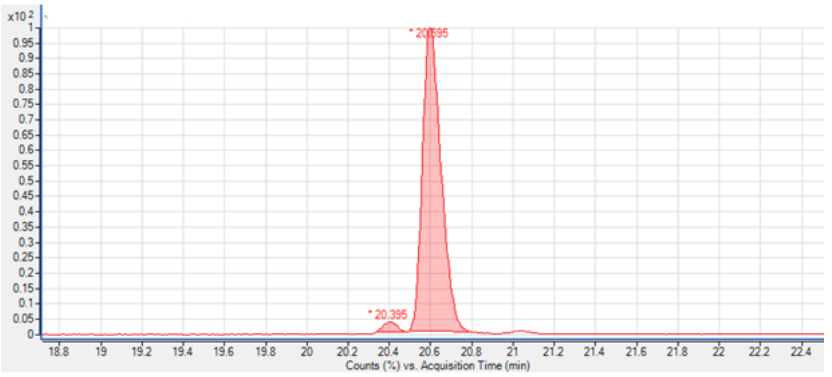
RT	Area	Area %
24.995	14019723.39	100
25.23	13974846.02	99.68



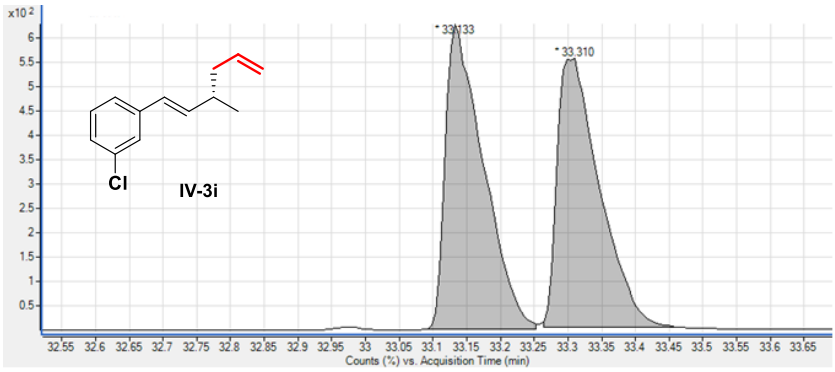
RT	Area	Area %
25.001	1443714.59	2.72
25.121	53022364.37	100



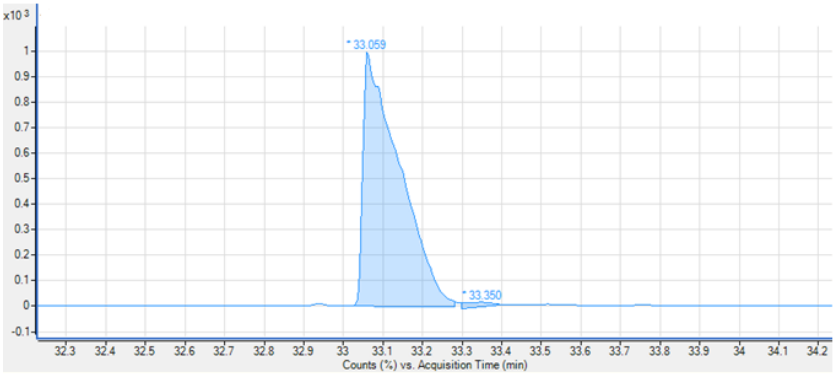
RT	Area	Area %
20.297	14063493.84	100
20.543	13724949.8	97.59



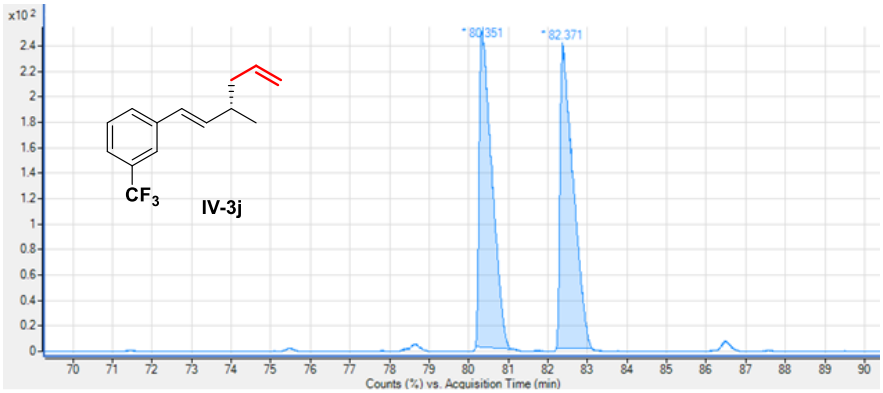
RT	Area	Area %
20.395	190108.33	2.46
20.595	7712311.19	100



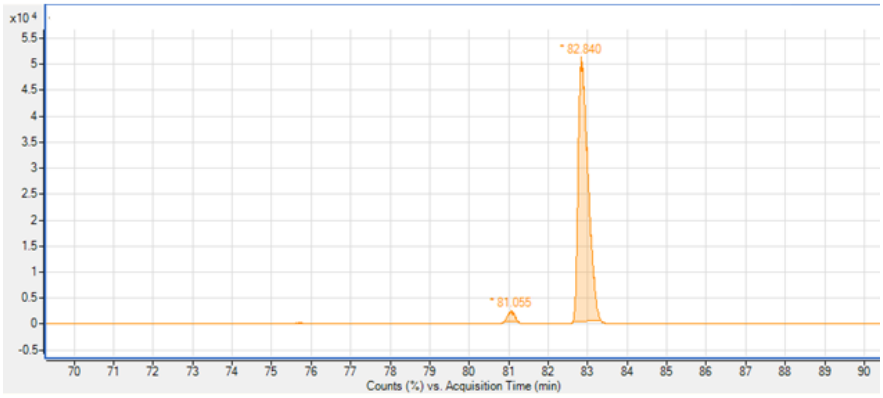
RT	Area	Area %
33.133	40621873.49	100
33.31	40045852.44	98.58



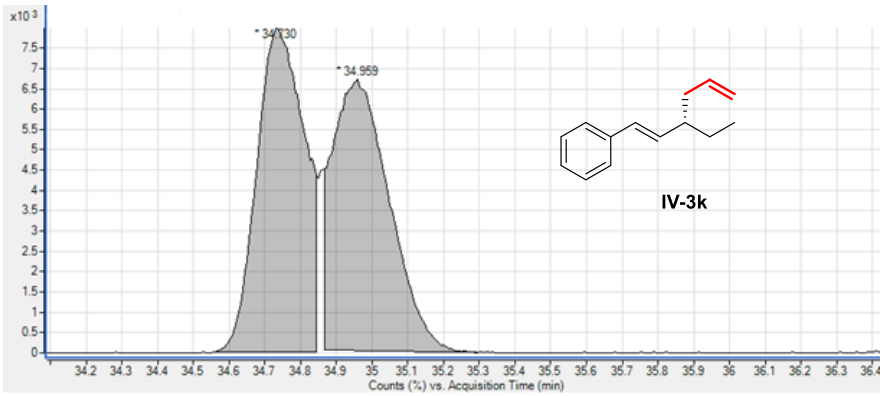
RT	Area	Area %
33.059	119136930.98	100
33.35	1682617.75	1.41



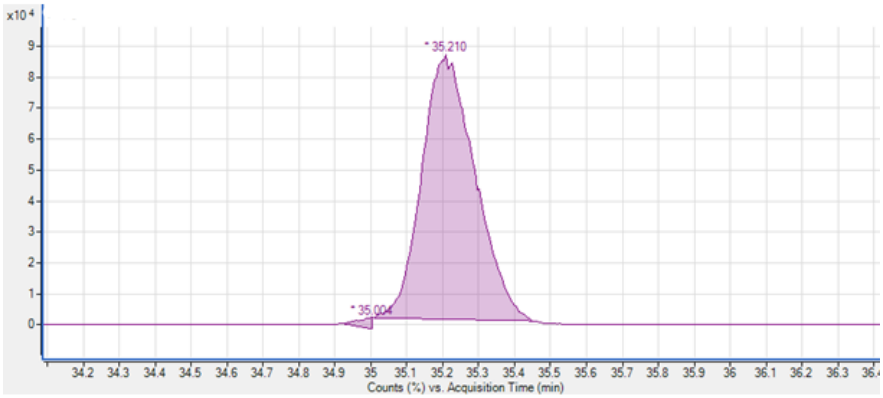
RT	Area	Area %
80.351	6123646.5	100
82.371	6062614.17	99



RT	Area	Area %
81.055	60224.8	2.7
82.84	2233696.25	100

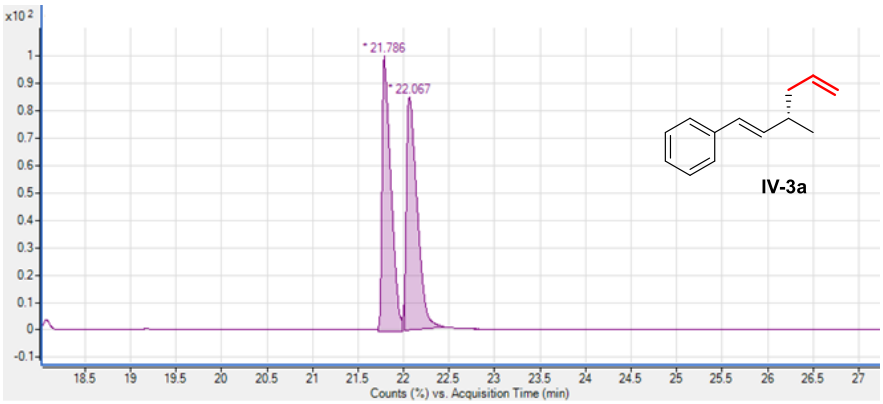


RT	Area	Area %
34.73	2060557.52	99.56
34.959	2069594.16	100

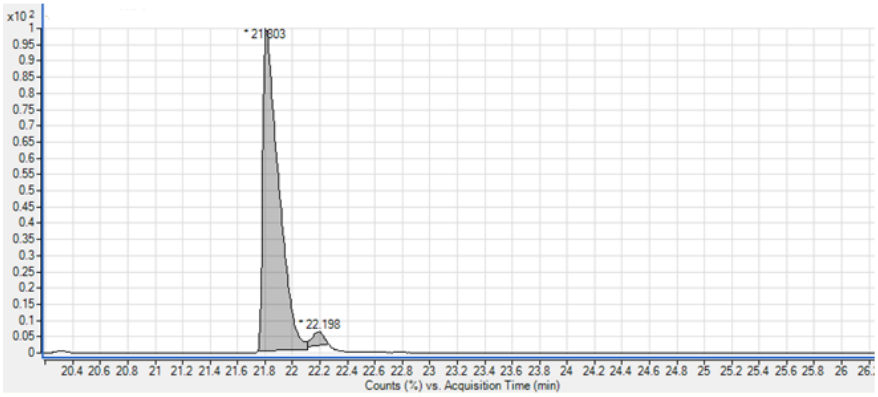


RT	Area	Area %
35.004	19885.64	1
35.21	1981570.39	100

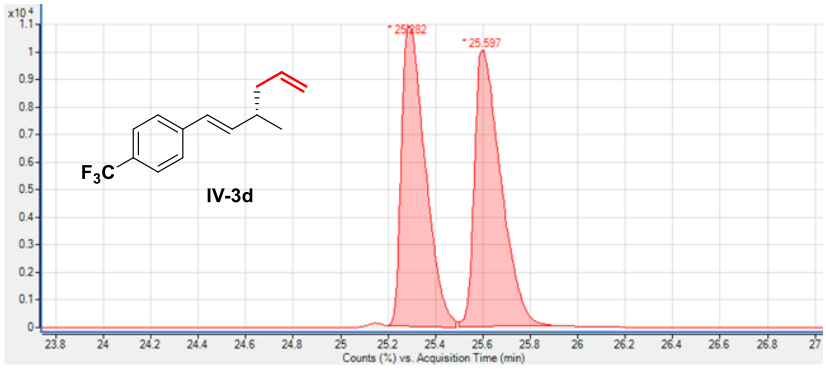
4.8.2. 1,5-dienes **IV-3** from **IV-2**.



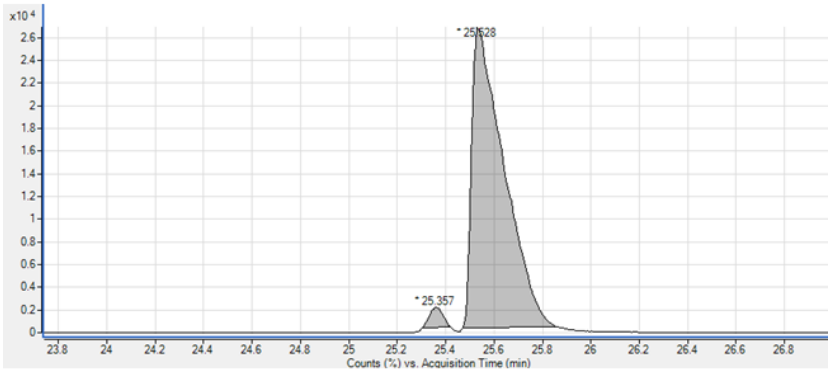
RT	Area	Area %
21.786	21275468.52	97.46
22.067	21830539.4	100



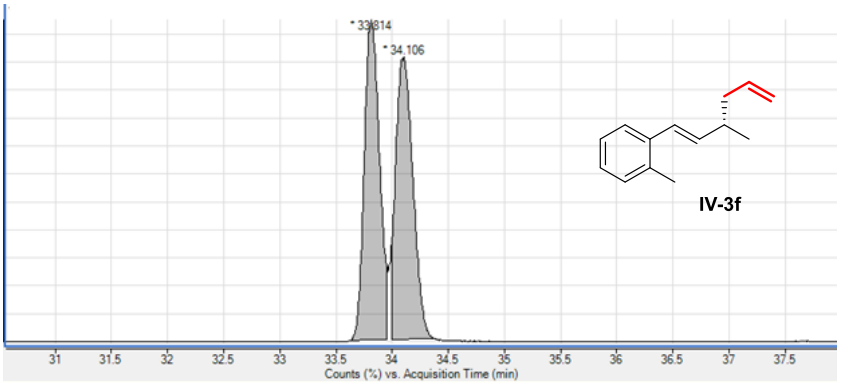
RT	Area	Area %
21.803	31198260.4	100
22.198	971547.33	3.11



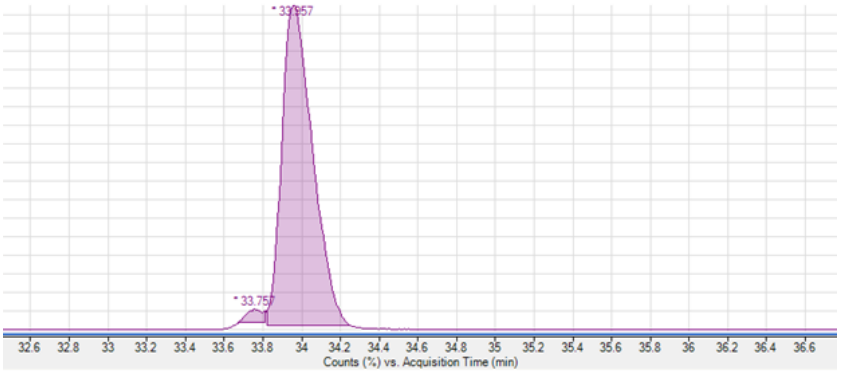
RT	Area	Area %
25.282	11588592.45	97.93
25.597	11833540.38	100



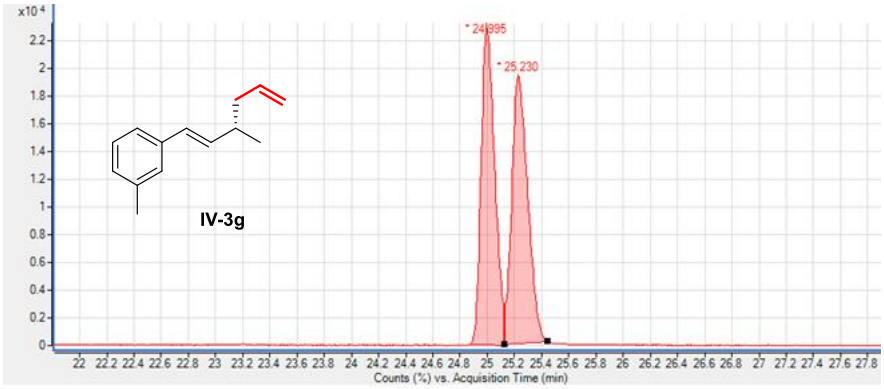
RT	Area	Area %
25.357	714391.19	2.73
25.528	26137582.63	100



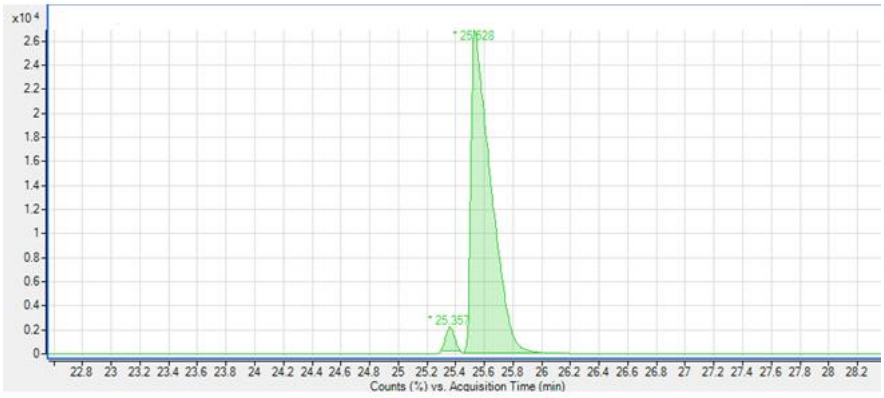
RT	Area	Area %
33.814	2054580.35	100
34.106	2052644.09	99.91



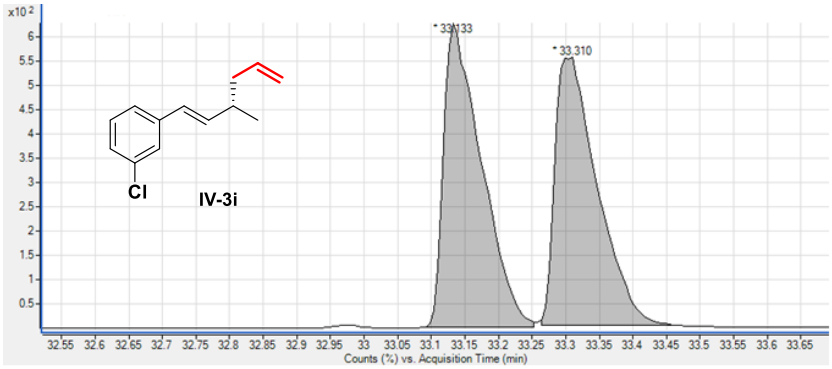
RT	Area	Area %
33.757	115772.22	2.16
33.957	5367106.44	100



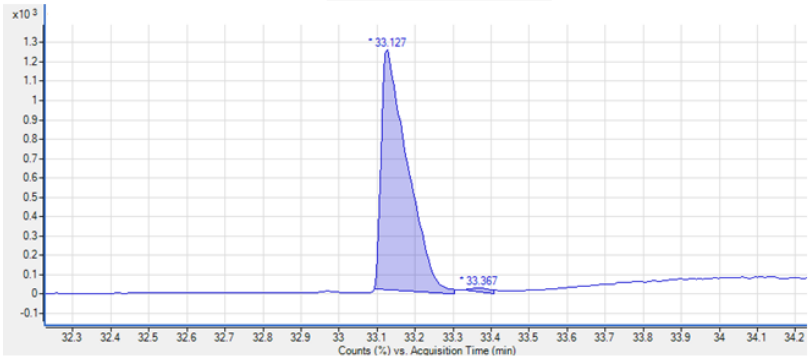
RT	Area	Area %
24.995	14019723.39	100
25.23	13974846.02	99.68



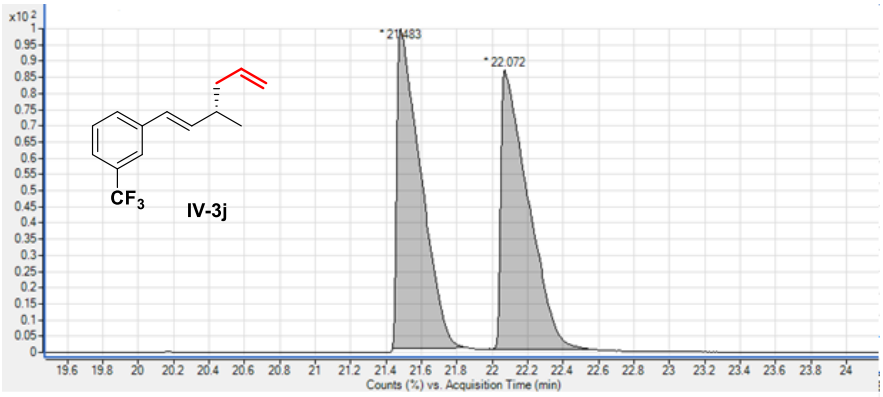
RT	Area	Area %
25.357	850002.67	3.14
25.528	27104224.16	100



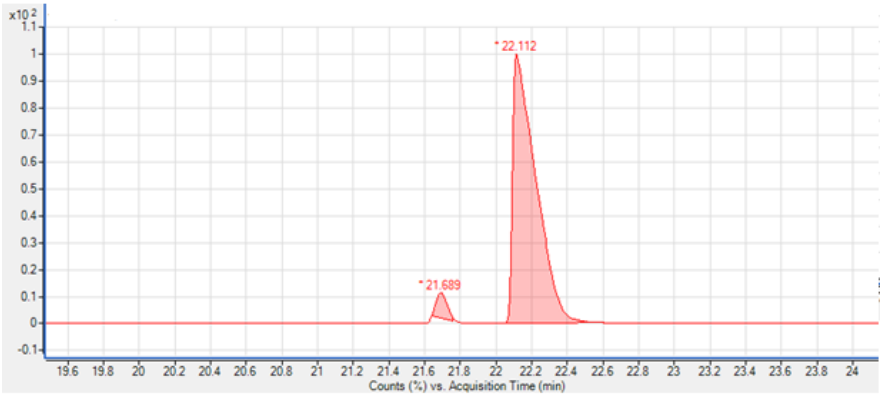
RT	Area	Area %
33.133	40621873.49	100
33.31	40045852.44	98.58



RT	Area	Area %
33.127	55095670.06	100
33.367	659798.31	1.2



RT	Area	Area %
21.483	29684834.69	100
22.072	29352942.1	98.88



RT	Area	Area %
21.689	814879.79	4.36
22.112	18670499.66	100